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UNIVERSITY OF ALBERTA

PART A: HETEROCYCLIC ARYLOXYPROPANOLAMINES AS β-ADRENERGIC ANTAGONIST AGENTS

PART B: HETEROCYCLIC 1,2-EPOXYALKAN-3-ONES AS CYTOTOXIC AGENTS

by

© DEAN VO

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE
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IN

PHARMACEUTICAL SCIENCES
(MEDICINAL CHEMISTRY)

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EDMONTON, ALBERTA
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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled "PART A: HETEROCYCLIC ARYLOXYPROPANOLAMINES AS β-ADRENERGIC ANTAGONIST AGENTS PART B: HETEROCYCLIC 1,2-EPOXYALKAN-3-ONES AS CYTOTOXIC AGENTS" submitted by DEAN VO, in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Pharmaceutical Sciences (Medicinal Chemistry).

E. E. Knaus
(Supervisor)

(External examiner)

Date: September 7, 1990

ABSTRACT

In part A, the aryloxypropanolamine class B compounds, which are considered to be an important chemical group of β-adrenergic blocking agents, have the general structure $R^1\text{-O-CH}_2\text{-CH(OH)-CH}_2\text{-NH-R}^2$. Most investigations to design new β-blockers have involved modification of the R^1 and R^2 substituents. The discovery of propranolol (**7**), and its extensive structural modifications, provided a large number of compounds having greater activities and selectivities. The replacement of the aryloxy moiety of propranolol by a 1,2-, 1,4-, or 1,6-dihydropyridine ring system, that is stablized by a single electron-attracting 3-cyano, or 3-(4,4-dimethyloxazol-2-yl) substituent, afforded (**146-151**). Replacement of the NH-R^2 moiety of propranolol by a 1,2-, 1,4-, or 1,6-dihydropyridine ring system, that is stablized by a single electron-attracting 3-cyano or 3-(4,4-dimethyloxazol-2-yl) substituent, afforded (**171-178**) or (**179-184**). Replacement by an isoquinolone, 4-quinazolone or 1-(4-diphenylmethylpiperazinyl) ring afforded (**255-256**), (**259-260**) or (**222**) respectively. The R^1 substituent of (**222**) was a 5-quinolyl ring system. The test results indicate that the activity of these two series of compounds exhibited a weak β-adrenergic antagonist activity on both atria and trachea relative to propranolol and that they are non-selective β_1/β_2 antagonists. Structure-activity correlations suggest an oxygen atom with a free electron pair or an amino hydrogen substituent may be essential for an efficient β-adrenergic receptor interaction involving the free electron pair on the oxygen atom or hydrogen bonding. Other heterocyclic analogues of propranolol (**7**) were prepared that possess a 5-quinolyl (**211, 212, 213**), 4-quinolyl (**233a**), 2-quinolyl (**242a,b**), 2-pyrimidinyl (**245a,b**), or 2-isoquinolyl ring system (**248-251**). Some of these compounds exhibited potent and selective β-adrenergic antagonist activity. The test results indicate that these hetereocyclic analogues of propranolol (**7**) were generally equipotent on atria, when the R^2 substituent was isopropyl or t-butyl and less potent when the steric properties or lipophilicity of the R^2 substituent was increased, relative to

propranolol. These compounds were highly selective β_1/β_2 antagonists. Structure-activity correlations suggest an oxygen atom having a free electron may be essential for an efficient β-adrenergic receptor interaction since activity was reduced when the oxygen atom was attached to a electronegative heteroaryl group.

The effect of chirality upon β-adrenergic antagonist activity for (2R or 2S)-1-(quinol-5-yloxy)-3-alkylamino-2-propanols was investigated by the preparation of the (2R)-1-(quinol-5-yloxy)-3-alkylamino-2-propanols (**214, 215**) and (2S)-1-(quinol-5-yloxy)-3-alkylamino-2-propanols (**216, 217**). The test results indicate that compounds having the (R,S)-, or (S)-configuration were equipotent with propranolol on atria. In addition they were ten times more active, and more β_1/β_2-selective antagonists, than compounds having the (R)-configuration. The structural modification of (S)-(**216**), by replacement of the R^2 substituents by cyclohexyl (**218**), 1-(3-phenylpropyl)-(**219**), 2-indolyl-t-butyl (**220**), or (S)-α-methylbenzyl (**221**) was investigated to determine the effect of these R^2 substituent upon β-adrenergic antagonist activity. The test results indicate that these compounds (**218, 219, 220, 221**) exhibited weaker β-adrenergic antagonist activity than (**216**) but they possessed a high β_1/β_2-selectivity.

The β_1- and β_2-adrenergic antagonist activity of selected compounds were determined using the chronotropic and inotropic response of guinea-pig right and left atrium, and trachea respectively. The β_1- and β_2-antagonist activity was quantitated from the dose dependent displacement of the isoproterenol concentration-effect curve. The structure-activity relationships for β_1- and β_2-adrenergic antagonist activity have been described.

In part B, alkylating groups have been incorporated into many types of molecules among which heterocyclic compounds are well represented. There has recently been a considerable degree of pharmacological interest in 3,3'-epoxy-α,β-dialkylstilbenes and their corresponding oxides, α,β-epoxysulfoxides and methenomycins which contain an oxirane ring system activated by different electron-withdrawing groups such as phenyl, sulfonyl or carbonyl. A new class of oxiranes which are activated by a pyridine ring system and an alkyl carbonyl group (**27a,b,c,d** and **28a,b,c,d**) were synthesized and evaluated as cytotoxic agents to determine their structure-activity relationships (SARs) using the P388 Lymphocytic Leukemia screen. The Darzen's reaction of a 2-pyridinylcarboxaldehyde (**24**) with methyl bromoacetate afforded a 1:1 mixture of the *trans*-(**25**) and *cis*-methyl 3-(2-pyridinyl)-2,3-epoxypropanoate (**26**) stereoisomers. Subsequently, the reaction of a 1:1 mixture of (**25**) and (**26**) with a Grignard reagent (RMgX; a, R= n-butyl; b, R= n-hexyl; c, R= n-decyl; d, R= n-hexadecyl) afforded a mixture of *trans*-(**27a,b,c,d**) and *cis* -1-(2-pyridinyl)-1,2-epoxyalkan-3-ones (**28a,b,c,d**) which were separated.

The pharmacological test results obtained indicated that the stereochemistry (*cis* and *trans*) of the oxiranyl substituents and/or size of the alkyl substituents of (**27a,b,c,d**) and (**28a,b,c,d**) are determinants of cytotoxic activity. The test results suggest that the increased steric effect of alkyl substituents is responsible for the greater activity of the *cis*-isomer, relative to the corresponding *trans*-isomer since the lipophilicity of the alkyl substituents is not expected to be a significant determinant of activity.

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LIST OF ABBREVIATIONS

ISA	Intrinsic sympathomimetic activity
ATP	Adenosine triphosphate
AMP	Adenosine monophosphate
bp	boiling point
cm	centimeter
^oC	degrees Celsius
CA	Carbachol
$CDCl_3$	deuterochloroform
CCl_4	carbon tetrachloride
CSR	chiral shift reagent
DMSO-d_6	hexadeuterodimethyl sulfoxide
h	hour
^{1}H nmr	proton magnetic resonance
INA (ISO)	Isonoradrenalines (isoproterenol)
Ir	infrared
mg	milligram
min	minute
mL	millilitre
mmol	millimole
ms	mass spectrum
S_N1	Substitution nucleophilic unimolecular
S_N2	Substitution nucleophilic bimolecular
tlc	thin layer chromatography
TMS	tetramethylsilane

PART A

" HETEROCYCLIC ARYLOXYPROPANOLAMINES AS β-ADRENERGIC ANTAGONIST AGENTS"

1.0.0.0.0 INTRODUCTION.

1.1.0.0.0 NOREPINEPHRINE AND ADRENERGIC RECEPTORS.

1.1.1.0.0 A DESCRIPTION OF THE NERVOUS SYSTEM.

The nervous system can be conceptually divided into the central and peripheral nervous systems, as illustrated in Figure 1. The peripheral nervous system can be further subdivided into the autonomic and somatic nervous systems. Both systems which are controlled by higher centers present in the brain, are stimulated by neurotransmitter release.

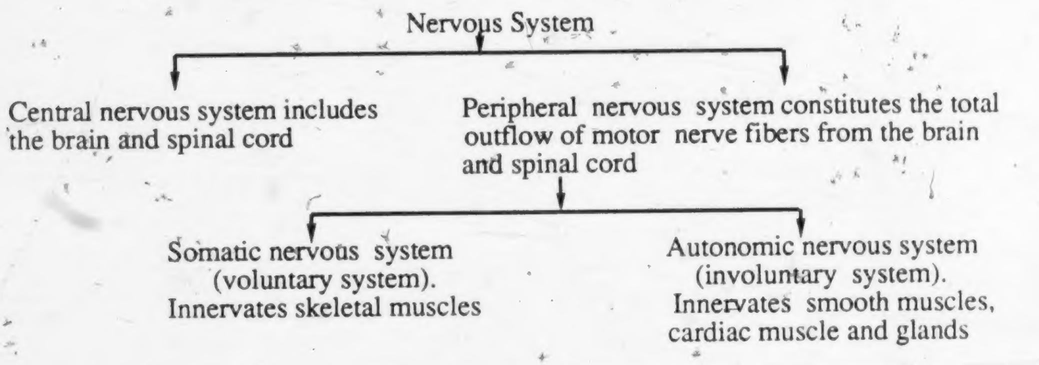
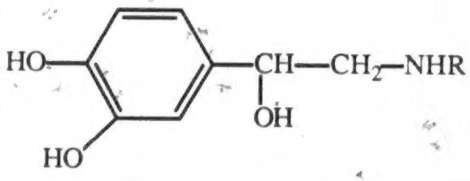

Nervous System
Central nervous system includes the brain and spinal cord
Peripheral nervous system constitutes the total outflow of motor nerve fibers from the brain and spinal cord
Somatic nervous system (voluntary system). Innervates skeletal muscles
Autonomic nervous system (involuntary system). Innervates smooth muscles, cardiac muscle and glands

Figure 1. **CLASSIFICATION OF THE NERVOUS SYSTEM**

1.1.2.0.0.THE ADRENERGIC NEURONAL SYSTEM.

The branch of the autonomic nervous system in which norepinephrine (**1a**), and to a lesser extent epinephrine (**1b**), act as neurotransmitters between a nerve ending and the effector muscle is known as the adrenergic nervous system. The adrenergic nervous system plays an important role in regulating many physiological functions including blood pressure, heart rate and force, gastrointestinal motility and bronchial tone[1].



1

1a) Norepinephrine R= H

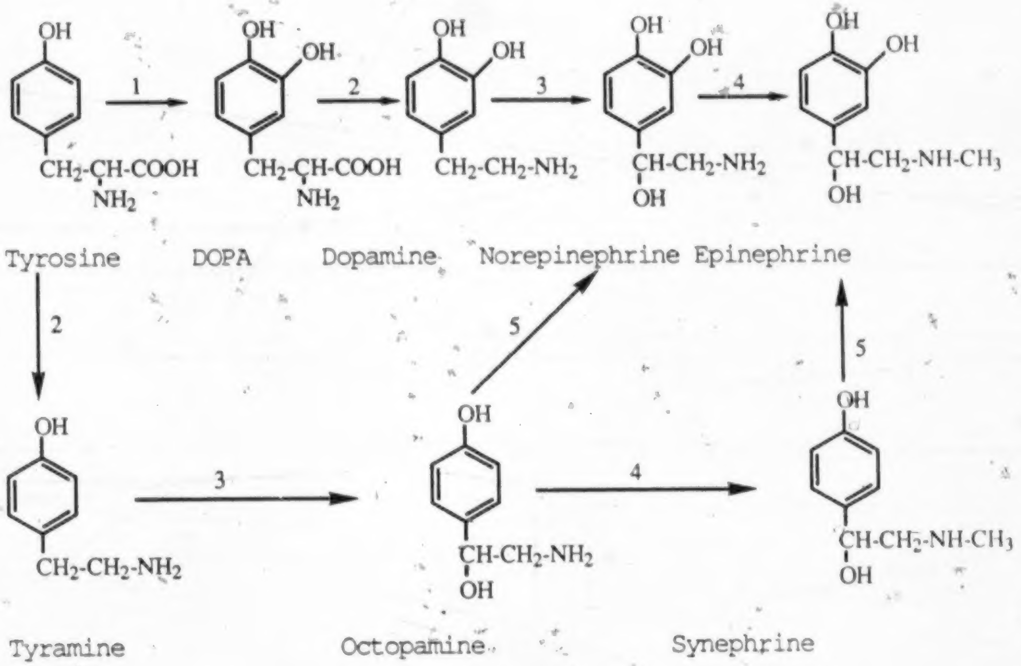
1b) Epinephrine R= CH_3

1c) Isoproterenol R= $CH(CH_3)_2$

The adrenergic nervous system, which is also called the sympathetic nervous system, is located in both peripheral and central areas. Peripherally, all organs are innervated by either the adrenergic or cholinergic systems. In most cases the adrenergic action of the peripheral nervous system is opposite to the cholinergic effects. Centrally, the two system can be distinguished, (1) the noradrenergic pathways which are primarily located in the locus ceruleus, a deeply pigmented small cell group, involved in behaviour, mood, and sleep; (2) the adrenergic pathways which use epinephrine as a neurotransmitter, have been explored only recently. The functional role of adrenergic and noradrenergic neurons can be assessed by selective destruction of these neurons[2a] or by radioligand studies[2b].

1.1.3.0.0 BIOSYNTHESIS OF CATECHOLAMINE NEUROTRANSMITTERS.

The adrenergic system utilizes neurotransmitters belonging to the class of substances known as catecholamines. Some biogenetically related catecholamines and the pathways leading to their biosynthesis are shown in Figure 2[3,4,5].


Tyrosine
DOPA
Dopamine
Norepinephrine
Epinephrine
Tyramine
Octopamine
Synephrine
1
2
3
4
5

Enzymes involved:

1 Tyrosine hydroxylase

2 Aromatic amino acid decarboxylase

3 Dopamine β-hydroxylase

4 Phenylethanolamine N-methyltransferase

5 Catechol-forming enzyme

Figure 2. Biosynthesis of Catecholamine Neurotransmitters.

1.1.4.0.0 ADRENERGIC RECEPTORS.

Adrenergic receptors[6,7] have been studied extensively using pharmacological methods, although little is known regarding their biochemistry. The concept that catecholamines bind to specific receptors in various tissues to initiate physiological responses was first suggested by Langley[8]. Langley further proved that receptors for epinephrine may contain substances which excited or inhibited the physiological processes. This hypothesis was also supported by a study by Dale[9] which showed that the excitatory actions of epinephrine were blocked by ergot, but the inhibitory effects were not, suggesting the existence of two types of receptors for epinephrine. Ahlquist[10] investigated the effects inhibited by six drugs that could stimulate the adrenergic system, which showed differences in the order of responsiveness. In one case, norepinephrine was the most active and isoproterenol (**1c**) was least active. However in other cases, the potency order was reversed, where isopreterenol was the most active. On the basis of these results, Ahlquist postulated the existence of two types of adrenergic receptors designated as α and β (Figure 3). α-Receptors are generally excitatory and mediate a constrictive effect on vascular, uterine and intestinal muscle upon stimulation by α-agonists. α-Receptors respond to different adrenergic agonists where the potency order is epinephrine > norepinephrine > isoproterenol. Evidence for the existence of a heterogeneous class of postsynaptic α-receptors in vascular smooth muscle was recently reported[11] that opens up additional approaches for drug development.

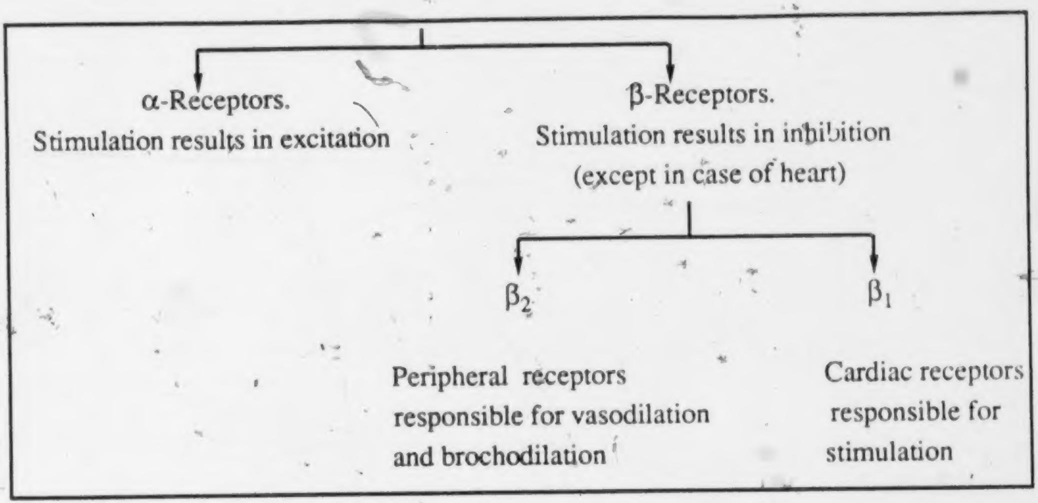

α-Receptors.
Stimulation results in excitation
β-Receptors.
Stimulation results in inhibition
(except in case of heart)
β_2
β_1
Peripheral receptors
responsible for vasodilation
and brochodilation
Cardiac receptors
responsible for
stimulation

Figure 3. Classification of adrenergic receptors.

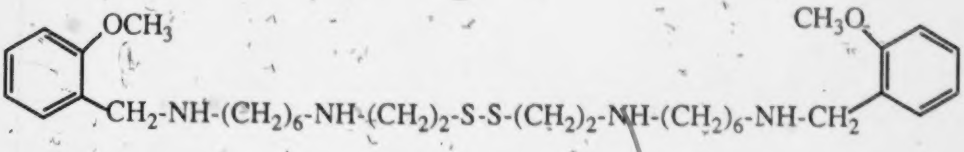
β-Receptors are usually inhibitory on smooth muscle but stimulate the myocardium by adrenergic agonist drugs. Their sensitivity to drugs is isoproterenol > epinephrine > norepinephrine. β-Adrenergic receptors have been further subdivided[12] into β_1- and β_2-receptor subtypes. β_1-Receptors which are present in heart, induce positive chronotropic (rate), dromotropic (conduction) and inotropic (contractility) effects. β_2-Receptors located in blood vessels and bronchi produce dilation of these structures. Liver β-adrenoceptors also belong to the β_2-adrenoceptor subtype[13,14]. The major differences between these two receptor subtypes is that norepinephrine exhibits a potent activity at β_1-adrenergic receptors, whereas norepinephrine exhibits a weak effect at β_2-adrenergic receptors. The advent of subtype-selective agonists and antagonists also provides evidence that both subtypes can be present in the same tissue such that cardiac responses in many species can be evoked by stimulation of either the β_1- or β_2-adrenoceptor[15-20]. The location of α- or β-receptors is not tissue specific since many organs contain both α- and β-adrenoceptors, although one type usually predominates. The predominant receptors present in human cardiac tissues are β_1-receptors, although β_2-receptors are also present in right[21-24] and left atrium[25,23]. In addition to the β_1- and β_2-subtypes, a third adrenergic receptor subtype has been isolated from a human gene that encoded for it that is referred to as a "β_3-adrenergic receptor". A β_3-adrenergic receptor has been implicated in the control of various metabolic processes of catecholamines[26].

1.1.4.1.0 PROPERTIES OF THE α-RECEPTOR.

The properties of the α-receptor have been investigated[27]. The development and investigation of polyamine disulfides (**2**,**3**), a novel class of irreversible selective α-agonist,[28] opened up new possibilities to study α-receptors. Investigations using benextramine (**2**) analogues resulted in the provision a tentative hypothetical receptor model[29]. On the basis of drug selectivity, there is now considerable evidence for the existence of two α-adrenoceptor subtypes[30].

$$H_2N{-}(CH_2)_5{-}NH{-}(CH_2)_2{-}S{-}S{-}(CH_2)_2{-}NH{-}(CH_2)_5{-}NH_2$$

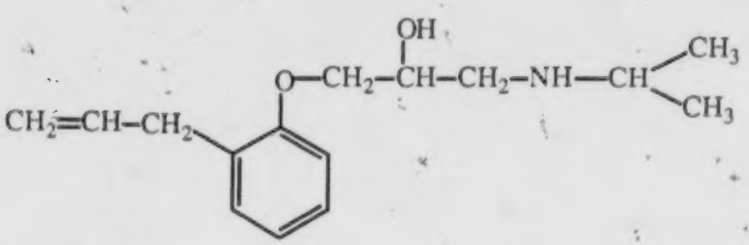
2



3 (Benextramine)

1.1.4.2.0 CHARACTERISTICS OF THE β-RECEPTOR.

The characteristics of the β-receptor are well-defined due to the many investigations carried out[31-43]. A various techniques including functional,[44-50] second-messenger,[51,52] radioligand binding,[54-56] and molecular biology studies[57-60] have been used to assess the properties of β_1- and β_2-adrenoceptors in human cardiac tissues. The results of these studies have been reviewed[61]. Functional studies were used to determine the inotropic and chronotropic responses for atrial or ventricular myocardium, whereas radioligand binding and adenylate cyclase studies provided information on the overall cardiac receptor population. The development of radioligands selective for β-adrenoceptors stimulated many investigations which resulted in their characterization, classification, and tissue localization[62]. The key to investigate properties of β-receptors successfully at the molecular level was the development of selective ligands. The two radiolabelled β-antagonists [^{3}H] alprenolol (**4**) and [^{125}I]iodohydroxybenzpindolol (**5**) were used for this purpose. Since the heart is composed of many different cell types, it is clearly important to identify which cells possess receptors and how they respond. The development of highly selective antagonists for β_1- and β_2-adrenoceptors and autoradiographic techniques[63-67] developed by Kuhar[68] facilitated the determination of β-adrenoceptor location in cardiac tissue.



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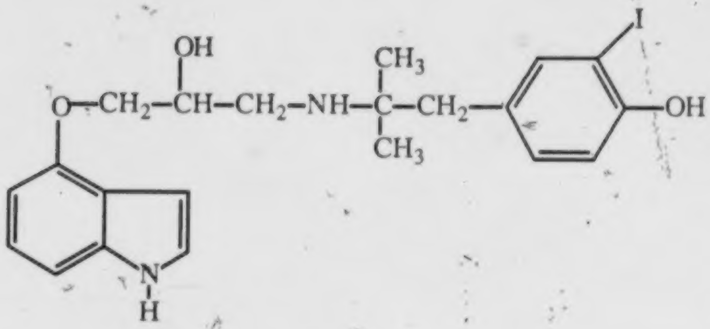


5

1.2.0.0.0 β-RECEPTOR AND ADENYLATE CYCLASE.

Three of the four subtypes (α_1, α_2, β_1 and β_2) of adrenergic receptors are linked to the enzyme adenylate cyclase, which generates the well-known second messenger 3',5'-cyclic adenosine monophosphate (cAMP)[51,69] as shown in Figure 4.

Adenylate cyclase catalyzes the conversion of adenosine triphosphate (ATP) to cyclic 3',5'-adenosine monophosphate (cyclic AMP). Cyclic AMP is released from the membrane-bound enzyme into the cell where it functions as a "second messenger". According to this concept, the β-adrenergic agonist acts as the "first messenger" since it carries information to the cell by interacting with β-receptors on the cell membranes.

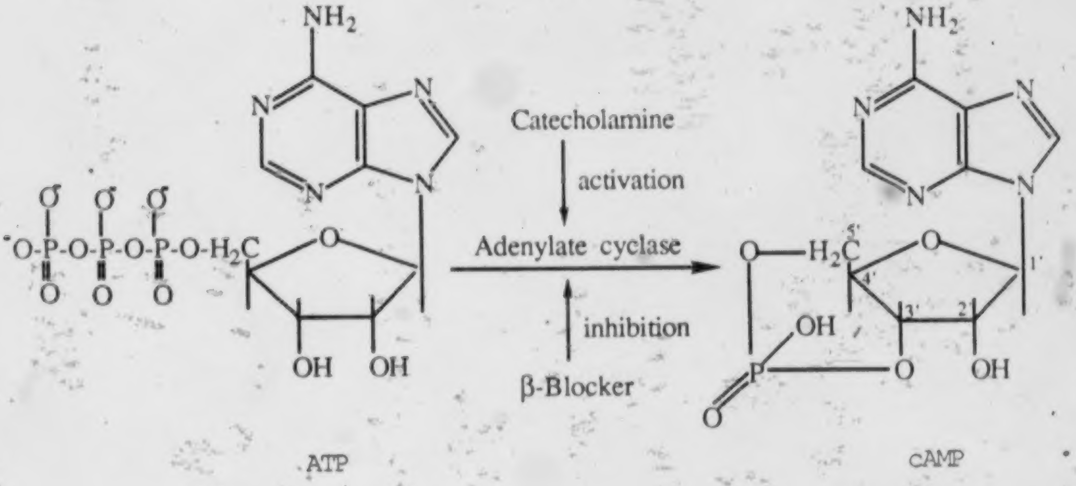


Figure 4. Adenylate cyclase converts ATP (Adenosinetriphosphate) into cyclic AMP.

The receptor-agonist interaction results in stimulation of adenylate cyclase and production of cyclic AMP, which acts as "a second messenger" by carrying the information to intracellular sites[70]. Cyclic AMP functions as the mediator of the action of the drug or neurotransmitter that originally interacted with the β-adrenergic receptor[71]. The enzyme adenylate cyclase is stimulated by catecholamines as well as a number of hormones including norepinephrine in virtually every tissue believed to contain pharmacologically defined β-receptors,[72,73] and is inhibited by α_2 receptors. The α_1 receptors mediate cellular calcium ion fluxes. Other receptors are also coupled to adenylate cyclase in either a stimulatory fashion, such as receptors for glucagon, prostaglandins, secretin or vasopressin; or in an inhibitory mode such as muscarinic or angiotensin receptors[74]. The coupling of receptors to adenylate cyclase is dependent upon a group of guanosine triphosphate (GTP) binding proteins called "G-proteins" that couple either stimulatory or inhibitory receptors, thus defining the "G_s" and "G_i" subtypes[75].

The intimate association of the β-receptor and adenylate cyclase is well supported by both qualitative and quantitative indices[76,73]. Although, stimulation of β-adrenoceptors produce a rise in cAMP levels in human left and right atrium, and ventricles;[23,47,49,77] it should also be noted that, in certain instances that a β-adrenergic response may occur without a measurable increase in cyclic AMP levels[78]. At one time it was proposed that adenylate cyclase itself was the β-adrenergic receptor. According to this concept, β-adrenergic agonists and antagonists interact directly with the catalytic site of adenylate cyclase to either activate or inhibit the enzyme[79]. However, it is now well established that the β-adrenergic receptor site that binds β-agonists and antagonists resides on a portion of the cell membrane that is separate from adenylate cyclase. The β-adrenergic receptor and adenylate cyclase are separated, membrane-bound macromolecules that appear to interact via a "coupling system" involving membrane lipids[80-83]. In adidition, guanyl nucleotides are involved in modulation of the binding of agonists and antagonists to the receptor[84]. A comparison of the potencies of agonists for stimulation of adenylate cylase and their affinities at β_1- and β_2-adrenergic receptors suggested close coupling of the enzyme to both receptor subtypes[49]. The most common β-agonists and β-antagonists activate adenylate cyclase in a stereospecific fashion[85].

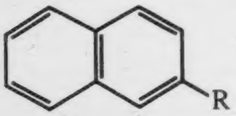
1.3.0.0.0 β-ADRENERGIC RECEPTOR BLOCKERS AS THERAPEUTIC AGENTS.

Ahlquist's classification of adrenergic receptors[10] into two distinct groups provided the basis for the emergence of a class of drugs which has made substantial impact on the understanding and the treatment of a wide spectrum of disease states. During the early ~~era of~~ β-blockers, their initial proposed therapeutic use was for the treatment of angina pectoris. The first effective β-blocker for the treatment of angina pectoris was pronethalol (**6**)[86,87]. Propranolol (**7**) was developed[89] shortly after clinical trials on pronethalol were terminated due to carcinogenic effects[88]. Propranolol was found to be beneficial for the treatment of angina pectoris[90]. Propranolol is one of the most widely investigated and extensively used β-blocking agents.

At the same time β-blockers were also being considered as anti-anginal agents, and other therapeutic applications in cardiovascular diseases. In animal studies, it was observed that pronethalol induced bradycardia which suggested β-blockers may be suitable for the treatment of arrhythmias[86]. Dichloroisoproterenol (DCI) (**8**) and pronethalol were found to exhibit antiarrhythmic activity against experimentally induced cardiac arrhythmias[91,92]. Subsequently, pronethalol was reported to exert effective antiarrhythmic activity in humans[93] which was also observed for propranolol[94,95]. β-Blockers were also considered for use in the treatment of myocardial infarction. In this respect, the first clinical trial using propranolol demonstrated that β-blockers reduced mortality in this patient population[96]. The observation that propranolol lowered blood pressure in patients who were being treated for angina[97] and the significant antihypertensive effect observed in clinical trials with propranolol[98,99] led to the use of β-blockers as primary drugs for the treatment of hypertension. An excellent review describing the use of β-blocking agents in hypertension has been published[100]. Numerous β-blockers have been developed and additional therapeutic indications have been suggested subsequent to the development of pronethalol and propranolol as clinically useful agents for the treatment of various cardiovacular disorders. The β-adrenoreceptor antagonists are safe and effective[101,102] drugs for the treatment of systemic hypertension,[103] arrhythmias,[104] angina pectoris,[105] myocardial infarction,[106] thyrotoxicosis,[107] open-angle gloucoma[108] and for prophylaxis against migraine headache[109]. Recently, the utilization of β-blockers for the treatment of migraine[110] headache has been reviewed[111]. Antimigraine activity is not a pharmacological action shared by all β-blockers, since this effect has been demonstrated clinically only for propranolol (**7**), timolol (**9**), metoprolol (**10**), nadolol (**11**) and atenolol (**12**).[111] The β_2-selective antagonist,[112] ICI-118551 (**13**) has undergone Phase II clinical trials as an antimigraine agent. β-Blockers have also been reported to be useful drugs for the treatment of anxiety,[113] and tremor[114].

1.4.0.0.0 ADVERSE EFFECTS OF β-BLOCKING DRUGS.

Although β-blocking drugs are for the most part highly effective, unexpected rises of blood pressure have been reported occasionally with atenolol (**12**),[115] oxprenolol (**14**),[116] propranolol (**7**)[117] and pindolol (**15**)[118]. There is no obvious reason for this unusual effect. There have been reports that patients have developed heart failure during propranolol chemotherapy[119]. Other β-blockers that exhibit ISA (intrinsic sympathomimetic activity) can also precipitate heart failure; this has been reported with alprenolol (**16**),[120,121] oxprenolol (**14**),[122] penbutolol (**17**)[121] and pindolol (**15**)[123]. Heart failure has also been reported with non-ISA β-blocking drugs such as timolol (**9**)[124]. A frequent side-effect of β-adrenergic blocking drugs is cool extremities[125]. There is some evidence that β_1-selective drugs are associated with a decreased incidence of cool extremities[126]. β-Receptor inhibition produces a significant increase in airway resistance in asthmatic individuals due to inhibition of sympathetic tone in bronchial smooth muscle[127]. Generally β_1-selective drugs exhibit less adverse effects than non-selective agents[128-130]. Other central nervous system side-effects that have been reported include sleep disturbances, insomnia, hallucinations, depression, delirium, headache[131,132]. Dreams occur more frequently with the lipid-soluble drugs[133,134] and there is some evidence that the β-blocking drugs which are lipid insoluble, such as atenolol (**12**),[133,135] or sotalol (**18**),[136] induce fewer central nervous system side effects.



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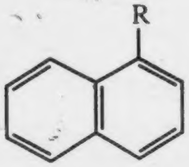

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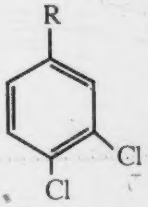
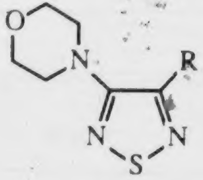


8

6 R= $CH_2CH(OH)CH_2NHCH(CH_3)_2$; **7** R= $OCH_2CH(OH)CH_2NHCH(CH_3)_2$,

8 R= $CH_2CH(OH)CH_2NHCH(CH_3)_2$.



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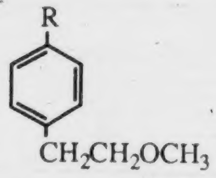
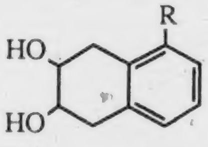
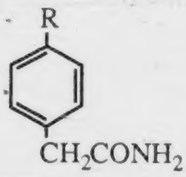

R
CH2CH2OCH3

10



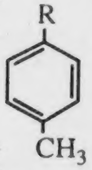
11



12

9 R= $OCH_2CH(OH)CH_2NHC(CH_3)_3$ **11** R= $OCH_2CH(OH)CH_2NHC(CH_3)_3$

10 R= $OCH_2CH(OH)CH_2NHCH(CH_3)_2$, **12** R=$OCH_2CH(OH)CH_2NHCH(CH_3)_2$



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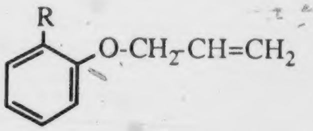
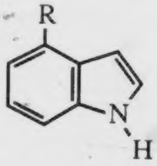
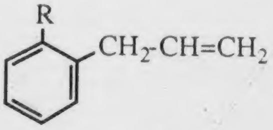

R
O-CH2-CH=CH2

14



15

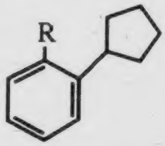


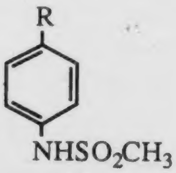
16

13 R= $OCH_2CH(OH)CH(CH_3)NHCH(CH_3)_2$

14 R= $OCH_2CH(OH)CH_2NHCH(CH_3)_2$ **16** R= $OCH_2CH(OH)CH_2NHCH(CH_3)_2$

15 R= $OCH_2CH(OH)CH_2NHCH(CH_3)_2$





17 R= $OCH_2CH(OH)CH_2NHC(CH_3)_3$ **18** R= $CH_2CH(OH)CH_2NHCH(CH_3)_2$

1.5.0.0.0 PHARMACOLOGIC PROPERTIES OF β-BLOCKING AGENTS.

All of the β-blockers, whether cardioselective or non-cardioselective that exhibit or do not exhibit ISA (intrisic sympathomimetic activity), now in common clinical use world-wide appear to be effective in lowering blood pressure in the majority of patients with essential hypertension. However the mechanism of their antihypertensive action is still uncertain[100,137]. There have been a number of suggested mechanisms by which β-adrenergic blocking drugs exert their hypotensive effect including a direct action on the central nervous system, adrenergic neuron blockage, anti-renin activity and an increase in vasodilator prostaglandins[138]. Although β-blockers inhibit renin release from the kidney, probably by an action on β_1-receptors,[139,140] there is generally a poor correlation between the decrease in plasma renin activity (PRA)[141] and reduction blood pressure during therapy. Other studies showed a much better correlation with sympathetic responsiveness,[142] or with a decrease in sympathetic nerve activity (SNA)[143-145]. This decrease in SNA may be an indirect reflex effect due to dampening sensory input to the CNS from the heart or to a direct central action[146]. The existence of central β-receptors has been investigated[147]. Direct injection of β-blockers into the brain lowers blood pressure but this is not necessarily due to blockade of β-receptors[148,149]. Although the antihypertensive potency of six β-antagonists in man correlated well with their ability to penetrate rat brain; this is not conclusive evidence for a central mechanism of action[150]. Although there have been many attempts to explain the antihypertensive action of β-blocking drugs, the mechanism is still controversial.

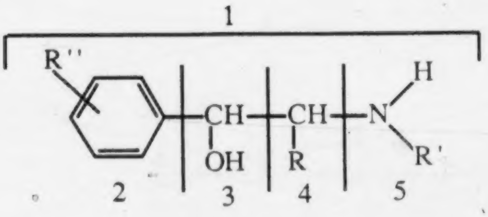
1.6.0.0 STRUCTURE-ACTIVITY RELATIONSHIPS OF ADRENERGIC AGENTS.

1.6.1.0.0 STRUCTURAL REQUIREMENTS FOR α- and β-ADRENERGIC ACTION.

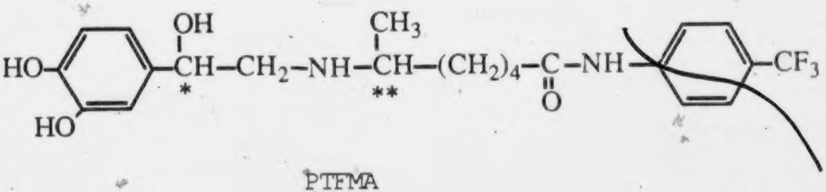
Variation of the N-substituent of norepinephrine (**1a**) demonstrated that increasing the bulk of the N-substitutent decreased activity at the α-receptor and increased activity at the β-receptor[151,152]. Derivatives possessing large substituents, particularly arylalkyl groups on the amino group, exhibit α-adrenergic blocking activity for, increase affinity and maintain intrinsic activity for β-receptors[153]. Fluorine substitution at the 2 or 6 positions of norepinephrine (NE) and related amines alters binding interactions with adrenoceptors where 2-F analogs are selective for α-receptors and 6-F analogs are selective for β-adrenoceptors[154,155,156]. The mechanism or fluorine-induced adrenergic selectivities has been investigated[157-159].

1.6.2.0.0 STRUCTURE ACTIVITY RELATIONSHIPS FOR β-ADRENERGIC AGONISTS[160].

The structural requirements for agonist activity at β-adrenergic receptors are: (1) a parent phenethylamine moiety; (2) a 3-hydroxy substituent, or preferably 3,4-dihydroxy substitution on the phenyl ring. Only one hydroxy substituent is required for β_2-agonist activity that is usually at C-4, but may also be located at C-3; (3) a β-hydroxy group with the D-(or R) configuration at the β-position for the "levo" enantiomer; (4) small R substituents H, CH_3, CH_3CH_2 may be located on this carbon without affecting agonist activity; (5) bulky alkyl or aralkyl R' groups; (6) the nitrogen must have at least one hydrogen.



Incorporation of a substituent containing a second asymmetric carbon onto the side chain amino group of isoproterenol (ISO) as illustrated for the p-trifluoromethyl-analide derivative (PTFMA) (**19**)[161] enhanced β-adrenergic agonist activity and receptor affinity. It was found that the RR diasteroisomer has a binding affinity for β-receptors roughly two orders of magnitude higher than that of (-)-(RS)-ISO[162].

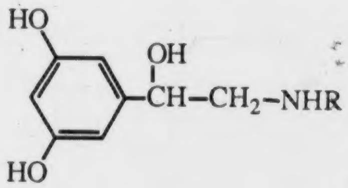


$HO-C_6H_3(OH)-\overset{OH}{CH}-CH_2-NH-\overset{CH_3}{CH}-(CH_2)_4-\underset{O}{\overset{\|}{C}}-NH-C_6H_4-CF_3$

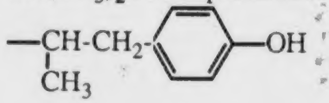
PTFMA

The catecholamine nucleus is the most significant structure required for the intrinsic activity at β-receptors. Elimination of the catechol hydroxyl groups from isoproterenol or substitution by other groups results in loss of intrinsic activity, although affinity for β-receptors[163] is maintained. Isoproterenol, (**1c**) a potent pure nonselective β-agonist, activates β_2-adrenergic receptors and stimulates β_1-cardiac adrenergic receptors to cause tachycardia. This cardiac stimulation has been implicated in the rise in asthma mortality thus indicating a need for a drug that has little β_1-activity. The development of β-stimulant bronchodilators, their pharmacology, evaluation, metabolism and structure activity relationships have been reviewed[163,164]. Structural analogues of isoproterenol continue to be synthesized and evaluated in the search for agents with fewer systemic side effects, more selectivity and longer duration of action than the prototype catecholamines. Introduction of new substituents and altering the positions of classical substituents on the benzene ring have provided compounds that are more resistant to catechol-o-methyl-transferase (COMT) and have a longer duration of action. Modification of the ethylamine side chain has provided compounds with increased β_2/β_1 selectivity[165].

Metaproterenol (**20**), the 3,5-dihydroxy positional isomer of isoproterenol exhibits a longer duration of action and greater selectivity than isoproterenol in patients with obstructive lung disease[166,167].

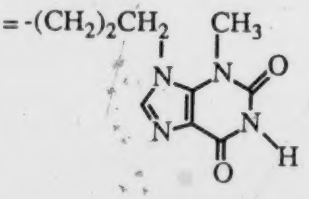


(20) R = $CH(CH_3)_2$, Metaproterenol

(21) R =


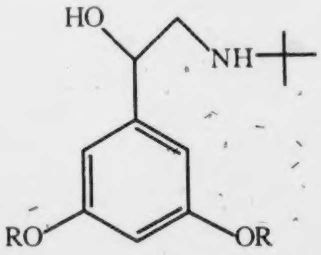
, Fenoterol

(22) R = $C(CH_3)_3$, Terbutaline

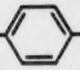
(23) R = $-(CH_2)_2CH_2$


Reproterol

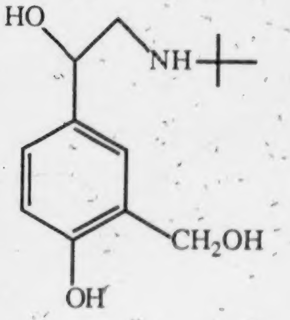
Fenoterol[168] (Th 1165a) (**21**), terbutaline (**22**),[169] reproterol (**23**),[170] which are analogues of metaproterenol (**20**), were investigated in asthamics and found to be more β_2-selective than ISO. The two lipophilic terbutaline ester prodrugs, bambuterol (**24**) and D 2438 (**25**) are more active and selective than terbutaline (**22**)[171].



(24) R = $CON(CH_3)_2$, Bambuterol

(25) R = CO–  –CO_2–$C(CH_3)_3$, D 2438

Replacement of the meta hydroxy substituent in the aryl ring of isoproterenol (**1c**) by a hydroxymethyl group which afforded salbutamol (**26**) is representative of a new type of β_2-adrenergic stimulant[172]. The duration of action and potency of salbutamol (**26**) are superior to that of isoproterenol (ISO)[173]. The pharmacology and toxicology of (**26**) have been studied extensively[174]. Two series of compounds have been investigated where the ethanolamine side chain is meta and para to the hydroxymethyl group. Significant adrenergic actions were exhibited by the former group of compounds where the ethanolamine and hydroxymethyl substituents were meta[175]. Similar results were observed for a "mixed catechol" compound which contains alkanesulfonamino and phenolic hydroxyl groups such as soterenol (**27**)[176].



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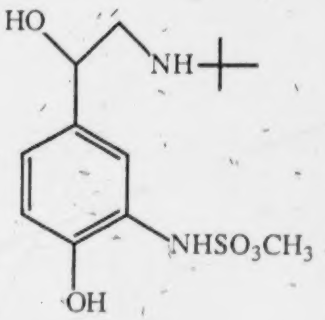
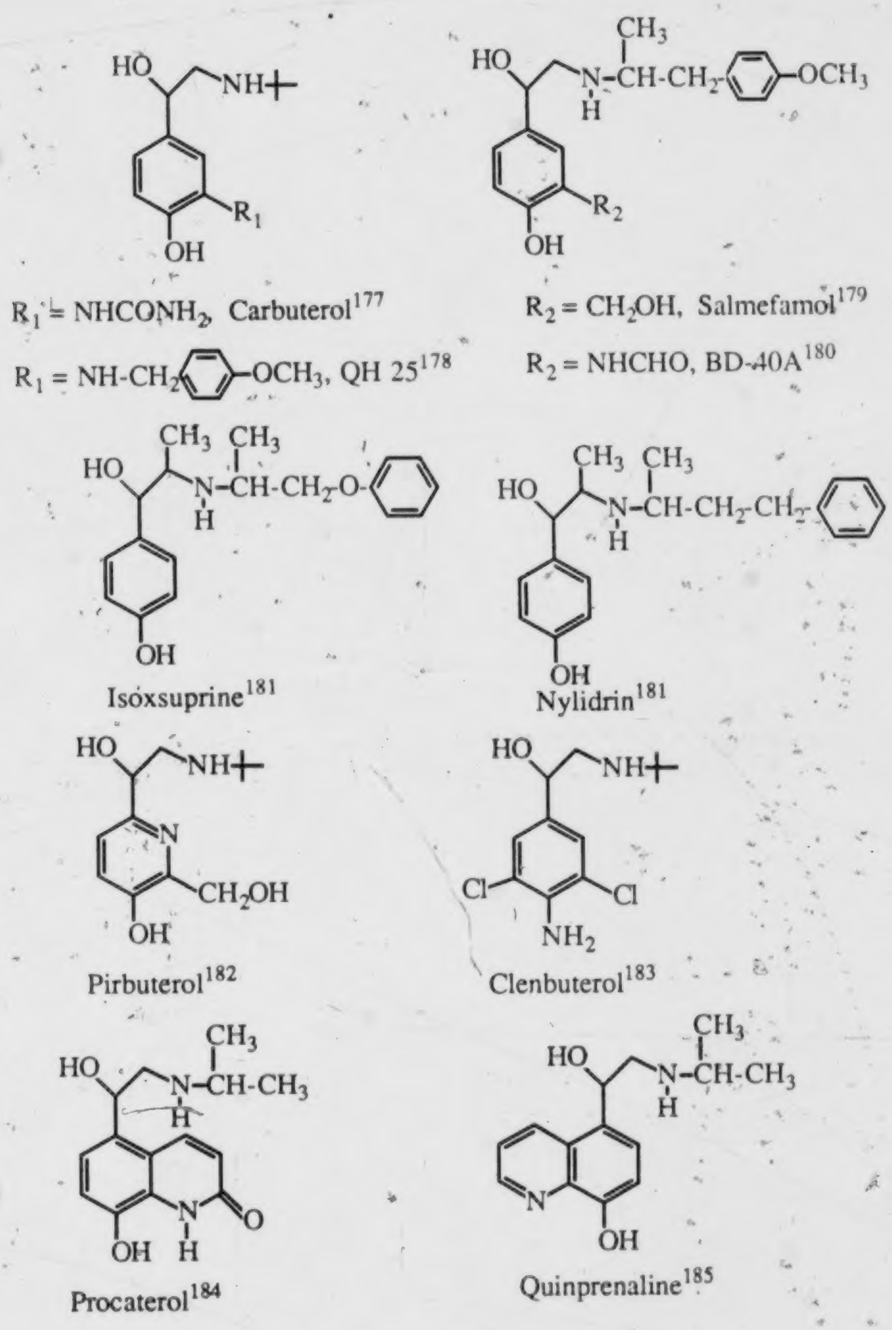


27

Most arylethanolamine β_2-selective agonists possess a para-hydroxy substituent on the aryl ring in conjugation with a variety of meta-substituents. Replacement of the phenyl ring by a pyridyl ring also provided compounds that are more β_2-selective agonists than ISO or salbutamol as summarized in Figure 5[177-185].

1.6.3.0.0 STRUCTURE-ACTIVITY RELATIONSHIPS FOR β-ADRENERGIC ANTAGONISTS[186,160].

β-Adrenergic antagonists acting as blockers at the receptor site require only those structural requirements that impart affinity for the receptor, but not intrinsic adrenergic activity. The general structural requirements for β-adrenergic antagonist drugs are similar to those for β-adrenergic agonists. The catechol hydroxyl groups are replaced by other groups.



R_1 = $NHCONH_2$, Carbuterol[177]

R_1 = NH-CH_2-⬡-OCH_3, QH 25[178]

R_2 = CH_2OH, Salmefamol[179]

R_2 = NHCHO, BD-40A[180]

Isoxsuprine[181]

Nylidrin[181]

Pirbuterol[182]

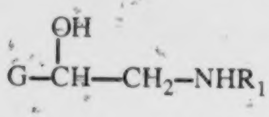
Clenbuterol[183]

Procaterol[184]

Quinprenaline[185]

Figure 5. Structures of β_2-selective agonists.

There are two major classes of β-adrenergic antagonist drugs which include the arylethanolamine class A and aryloxypropanolamine class B compounds.



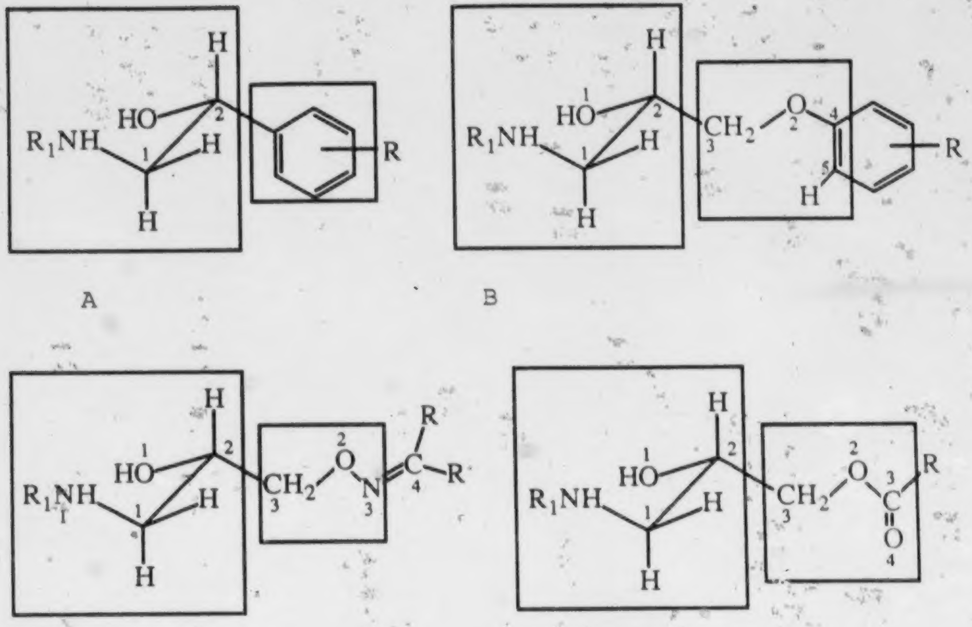
$$G-\overset{\displaystyle OH}{\overset{|}{C}}H-CH_2-NHR_1$$

A, G= Ar

B, G= $ArOCH_2$;   B', G= $RRC{=}NOCH_2$

C, G= $ArCOOCH_2$; C', G= $RCOOCH_2$

The difference between the two principle classes of β-blocking adrenergic drugs A and B illustrated above is the presence of the OCH_2 moiety located between the Ar ring and the ethanolamine group in type B derivatives. The $CH(OH)-CH_2-NHR_1$ moiety is associated with the drug's affinity for adrenergic receptors whereas, its stimulating or blocking properties are determined by the nature of the aryl group[187,188]. Several hypotheses have been proposed[187,189-195] to explain the similar pharmacological activity of the two classes of drugs and the mechanism by which the CH_2-O-Ar moiety of class B agents can substitute for the aromatic moiety (Ar) of class A compounds in the drug-receptor interaction. X-ray diffraction studies have shown,[196] as illustrated in Fig.6 that the C(3)-O(2)-C(4)-C(5) atoms of the class B drug define a plane, and the spatial relationship between this plane and the ethanolamine side chain is the same as that observed between the aromatic ring and the ethanolamine side chain in class A drugs.



A

B

B'

C, R = Aryl

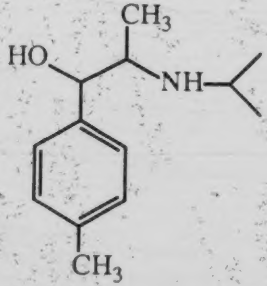
C', R= Alkyl

Fig 6. Perspective view of 2-arylethanolamine (A), 3-(aryloxy)propanol amine (B), 3-(iminooxy)propanolamine (B'), 3-(aroyloxy)propanol amine (C), and 3-(acyloxy)propanolamine (C') derivatives.

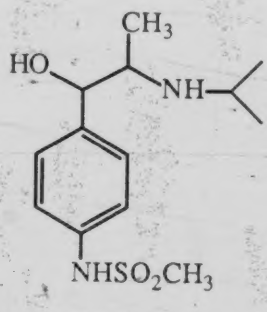
On the basis of this observation, it was hypothesized[197] that C(3)-O(2)-C(4)-C(5) moiety of class B adrenergic β-blocking drugs might in some way "simulate" the aromatic ring of class A drugs to serve as a "bioisostere"[198] of the Ar group. This hypothesis was subsequently supported[187,194,199] by quantum mechanical studies which indicated that the C(3)-O(2)-C(4)-C(5) structural feature of class B drugs and the aryl moiety of class A drugs possess a comparable "chemical reactivity". Further studies,[188,200,201,202] utilizing type B drugs, showed that a marked competitive β-blocking activity was also exhibited by compounds lacking aromatic groups. This lead to the development of "non-classical" β-blockers such as the aliphatic oxime ether derivatives of class B,[203,204,205] and propanolamine ester derivatives of class C[206,207,208,209] as illustrated in Figure 7.

1.6.4.0.0 ARYLETHANOLAMINE, β-ADRENERGIC BLOCKING AGENTS OF CLASS A.

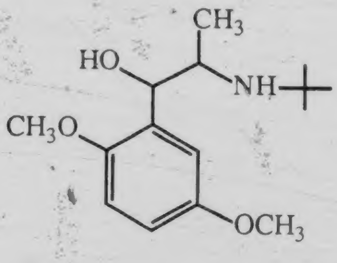
Most class A β-adrenergic blocking agents have been made by modification of the basic isoproterenol structure (**1c**). For example, replacement of catechol OH groups by Cl provided dichloroisoproterenol (DCI) (**8**),[210] whereas replacement of C-3 and C-4 hydroxyl substituents with fused phenyl ring system gave pronethalol (**6**),[86,87] which is a better blocker than DCI (**8**); small α-methyl substituent is a useful structural feature for β_2-selective blocking activity as reported for H35/25 (**28**),[211] metalol (**29**),[211] and butoxamine (**30**)[212].



(**28**) H 35/25[211]



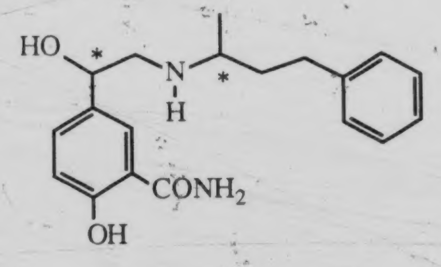
(**29**) Metalol[211]



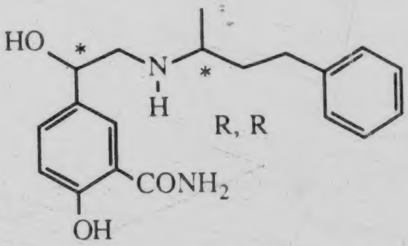
(**30**) Butoxamine[212]

Further modification of isoproterenol where the isopropyl group was replaced by an arylalkyl substituent, and the catechol meta OH group was substituted by a carboxamide moiety gave labetalol (**31**)[213,214,215] which was the first member of new a class of antihypertensive agents having both α- and β-adrenoceptor blocking properties[213]. Labetalol

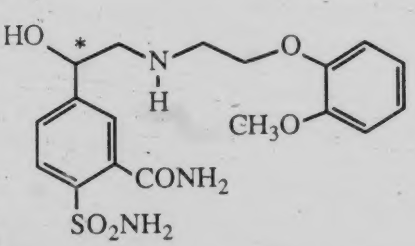
(**31**) possesses two chiral centers and the clinical formulation is comprised of equal proportions of 4 diastereomers (RR,RS, SR,SS). The individual diastereomers have recently been synthesized,[216] and were found to differ widely in their pharmacological profiles. The most potent β-adrenoceptor blocker is the RR-diastereomer, dilevalol (**32**)[217,218,219] The pharmacological properties of labetalol and its diastaromers has been reviewed[220]. Other structurally related arylethanolamines have also been shown to possess combined α- and β-adrenoceptor blocking properties such as amosulalol (**33**),[221] and medroxalol (**34**)[222]. Sulfinalol (**35**), which is structurally related to Labetalol (**31**), exhibits both β-agonist and direct vasodilating actions but not α-blockade[223]. Other structural modifications carried out on isoproterenol (**1c**) have provided a large number of potent β-blockers which are listed in Figure 7.



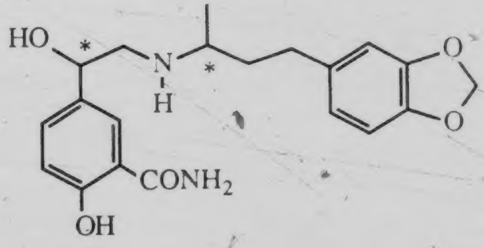
(**31**) Labetalol[213-215]



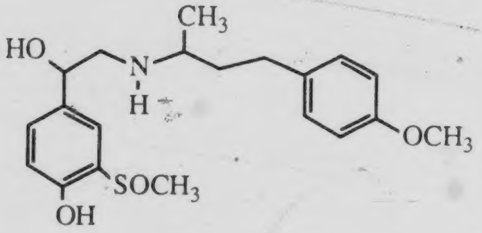
(**32**) Dilevalol[217-219]



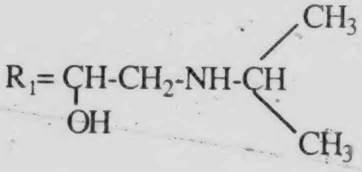
(**33**) Amosulalol[221]



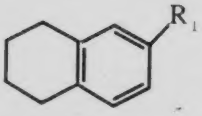
(**34**) Medroxalol[222]



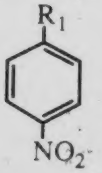
35 Sulfinalol[223]



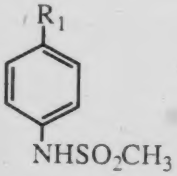
$$R_1 = CH(OH)-CH_2-NH-CH(CH_3)_2$$



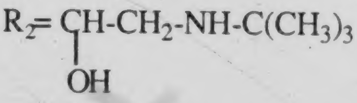
Butidrine[224]



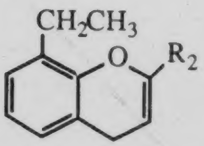
Nifenalol[225]



Sotalol[226]



$$R_2 = CH(OH)-CH_2-NH-C(CH_3)_3$$

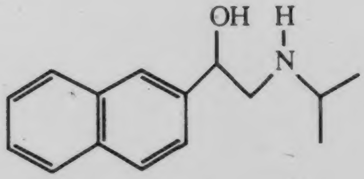


Bufuralol[227]

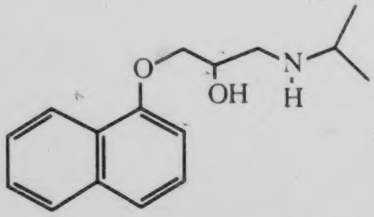
Figure 7. Some structures of class A β-adrenoceptor blocking agents.

1.6.5.0.0 ARYLOXYPROPANOLAMINE, β-ADRENERGIC BLOCKING AGENTS CLASS B.

The aryloxypropanolamine class B compounds are recognized as an important chemical group of β-adrenergic blocking agents[228,229]. Introduction of an oxypropanolamine group at the α-position of the naphthyl ring, relative to an ethanolamine side chain at the β-position of the naphthyl ring as in pronethalol (**6**) culminated in the introduction of propranolol (**7**)[230] which became known as a second generation β-blocker. The discovery of propranolol and extensive structure-activity relationships which were acquired, demonstrated a bioisosteric relationship between the arylethanolamine (A), and aryloxypropanolamine (B) classes of adrenergic agents. Nevertheless, there have been few systematic studies aimed at ascertaining the essential structural features for aryloxypropanolamine β-antagonists[231].



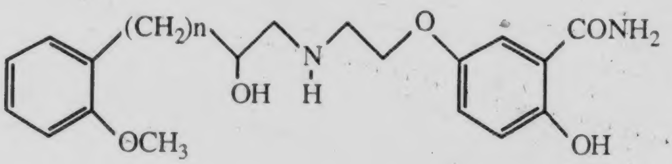
(6) Pronethalol



(7) Propranolol

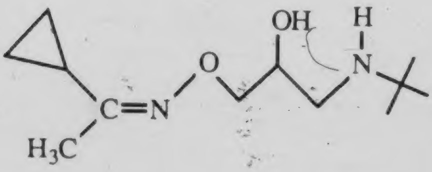
It is known[232] that replacement of the ethereal oxygen atom of propranolol by a methylene group reduced potency markedly (>100 times), thus indicating that this atom is directly involved in the binding to the receptor by means of its unshared electrons[233]. Recently, a group of compounds of general structure (**36**, n= 0-4) were reported[234] where the

β_1-blocking activity for the ethylene analog (n=2) was found to be surprising high (pA_2= 7.85).



36

It was concluded that an ethereal oxygen may be important with respect to affinity for the receptor, but is not an absolute prerequisite for potent β-blockade. It is also plausible that the electron donor effect of the ethereal oxygen enhances aryl group receptor binding. However, some potent class B' oxime ether β-antagonists such as falintolol (**37**)[235] and class C aroyloxypropanolamine β-antagonists such as (**38**) are known where the ethereal oxygen is not directly bonded to an aromatic ring.



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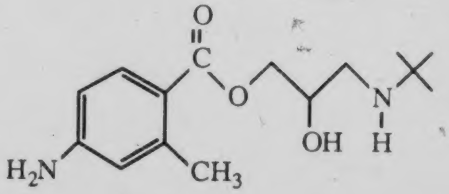

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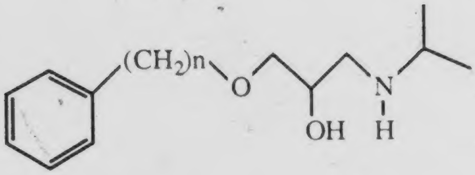
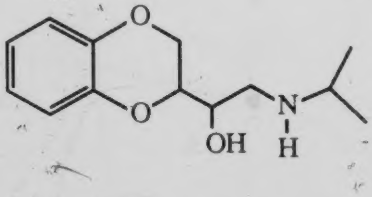
The interposition of aliphatic fragments between the aromatic ring and the oxypropanolamine side chain (**39**), reduces potency[236]. This result indicates the important distance between the aromatic ring and the aminoalcohol group.



39

Replacement of the naphthalene ring of propranolol (**7**) by quinoline, benzofuran, benzothiophene, indole, methylenedioxyphenyl or oxoxanthene did not appreciably alter β-blocker activity[237]. Likewise, replacement of the naphthalene ring of pronethalol (**6**) by indole, quinoline, phenothiazine, benzodioxan, dibenzofuran, or quinazoline caused little change in activity[238]. Other compounds, such as benzodioxanylethanolamines (**40**),[239] and (**41**);[240] and benzofuranylethanolamines (**42**),[241] and (**43**),[242] which are ring-closed *ortho*-substituted (aryloxy)propanolamines, act as β-blockers that exhibit antihypertensive properties.



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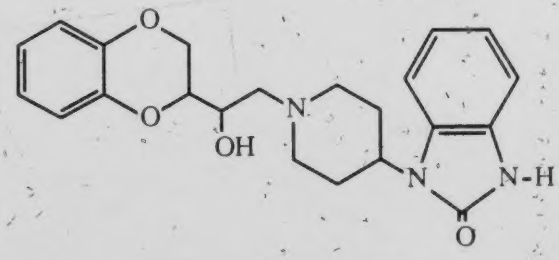

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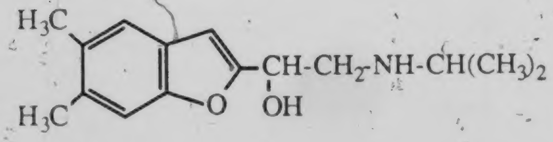

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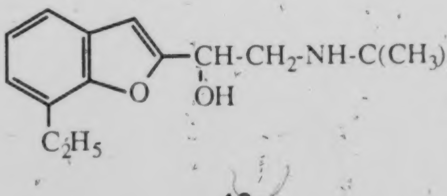

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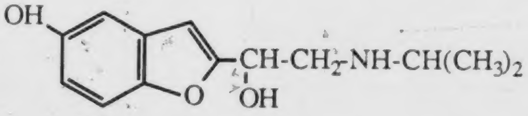
In contrast, to the β-antagonist (**42**), 5-hydroxy analog (**44**) was reported[243] to be a cardioselective adrenergic agonist with a high intrinsic activity.



44

The structural modifications carried out on propranolol (**6**) and its congeners have provided a large number of potent β-blockers, some of which are listed in Figure 8[244-271].

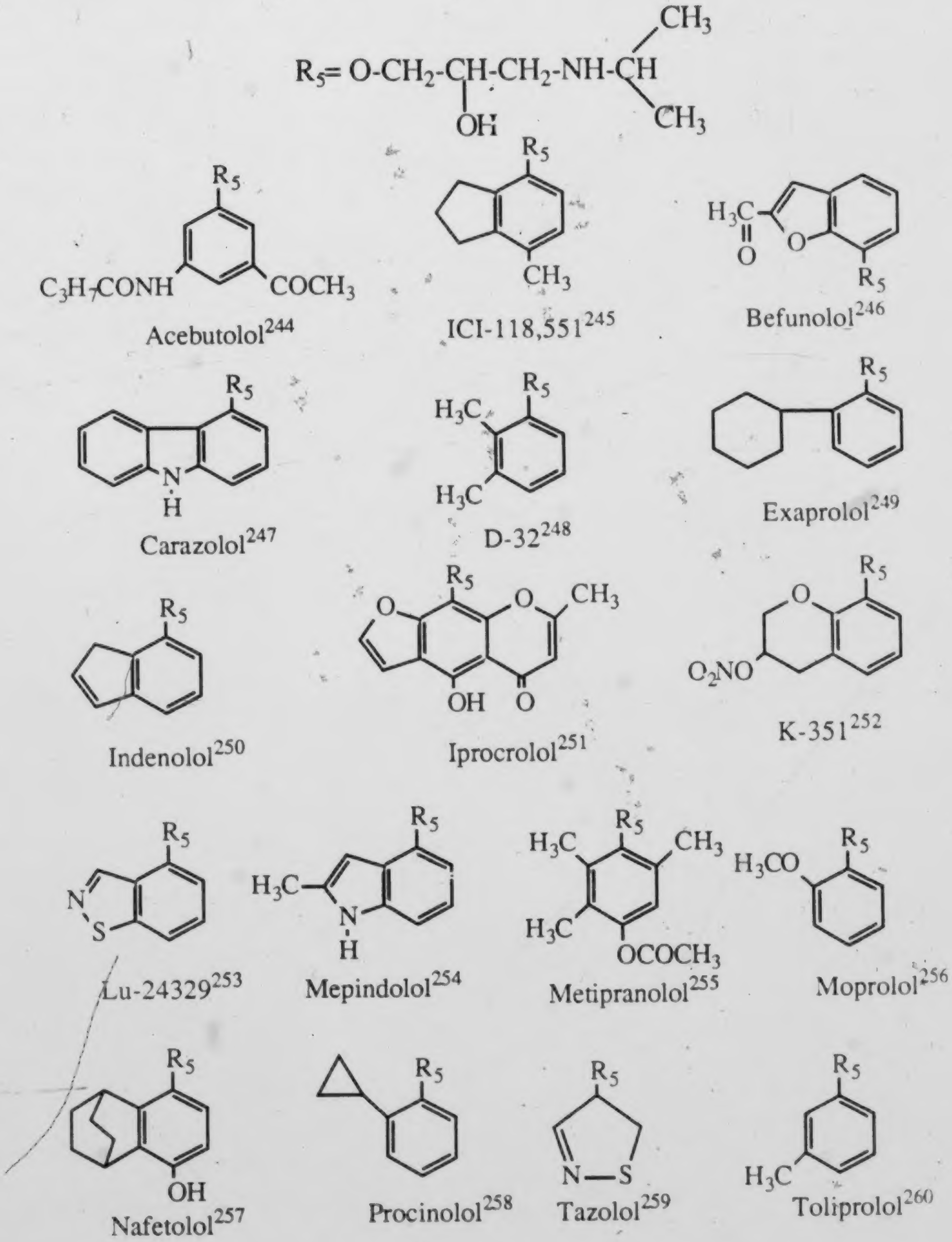
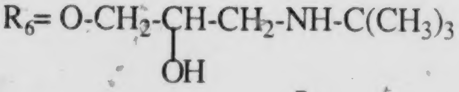
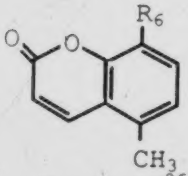

R$_5$= O-CH$_2$-CH-CH$_2$-NH-CH
OH
CH$_3$
CH$_3$
R$_5$
C$_3$H$_7$CONH
COCH$_3$
Acebutolol[244]
CH$_3$
ICI-118,551[245]
H$_3$C
O
Befunolol[246]
N
H
Carazolol[247]
D-32[248]
Exaprolol[249]
Indenolol[250]
OH
Iprocrolol[251]
O$_2$NO
K-351[252]
S
Lu-24329[253]
Mepindolol[254]
OCOCH$_3$
Metipranolol[255]
H$_3$CO
Moprolol[256]
Nafetolol[257]
Procinolol[258]
N—S
Tazolol[259]
Toliprolol[260]

Figure 8. Structures of β-blocking aryloxypropanolamine class.

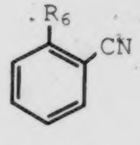
Figure 8. (cont.)



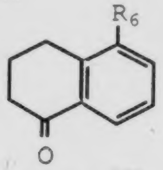
$$R_6 = O\text{-}CH_2\text{-}\underset{OH}{CH}\text{-}CH_2\text{-}NH\text{-}C(CH_3)_3$$



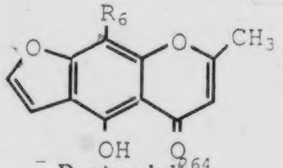
Bucumolol[261]



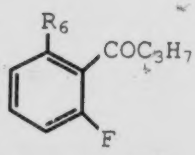
Bunitrolol[262]



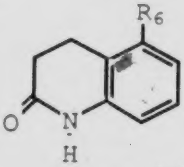
Bunolol[263]



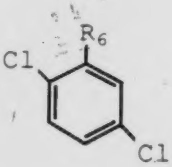
Butocrolol[264]



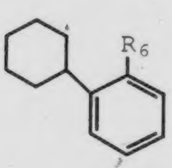
Butofilolol[265]



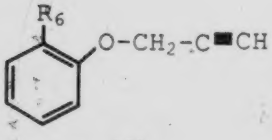
Carteolol[266]



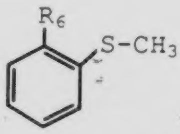
Cloranolol[248]



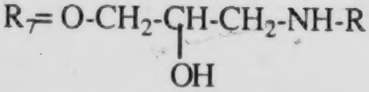
Exaprolol[267]



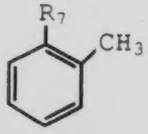
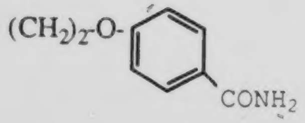
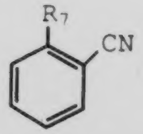
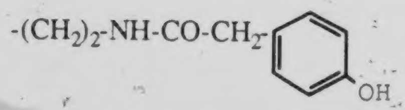
Pargolol[268]



Tiprenolol[269]

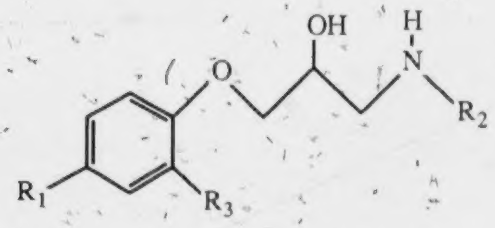


$$R_7 = O\text{-}CH_2\text{-}\underset{OH}{CH}\text{-}CH_2\text{-}NH\text{-}R$$

R_7	R	NAME
		Tolamolol[270]
		ICI-141,292[271]

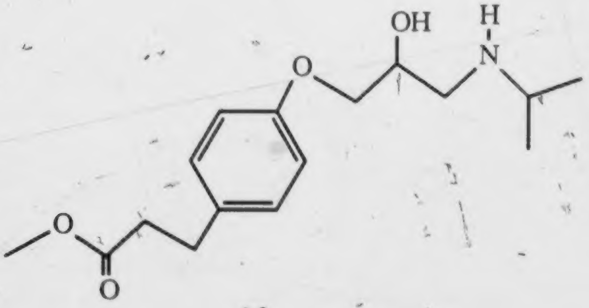
9

Most β-adrenergic blocking agents were found to be non-selective since they interacted with both β_1 and β_2-adrenergic receptors. The discovery of practolol **(45a)**[272] stimulated the search for β-adrenoceptor blockers having a higher affinity and selectivity toward the β_1-adrenoceptor. A significant enhancement in cardioselectivity can be achieved by the placement of (1) a polar substituent R_1 at the 4 position of the 3-aryloxy group present in 1-aryloxy-3-[(arylalkyl or alkyl)amino]propan-2-ols (**45**);[273] (2) certain arylalkyl or alkyl groups R_2 on the amino groups;[274] or (3) 1-methyl substitution in the propan-2-ol moiety[275]. Thus, the skillful simultaneous manipulation of R_1, and R_2 or R_3 along with the side chain substitution seems to give the highest available cardioselectivity. There is no definite pattern for substituents on the aromatic ring as both electron donating and electron withdrawing groups are present in active compounds. However, it has been observed that *para*-substitution in the aryloxy moiety appears to result in greater β_1-selectivity. For example, for practolol and its positional isomers, it has been observed that *para*-substitution on the aryloxy ring tends to give greater cardioselectivity than do the corresponding *ortho* isomers[276]. In case of esmolol (**46**), the cardioselectivity is attributed to the location of the ester in the *para* position since the *ortho* ester analog of esmolol is non-selective[283]. Esmolol is an ultra-short acting, cardioselective β-blocker with no intrinsic sympathomimetic activity. The capability of rapid reversal makes esmolol uniquely suitable for the acute management of supraventricular tachycardia, and the control of blood pressure and heart rate during surgery or other cardiac emergencies.



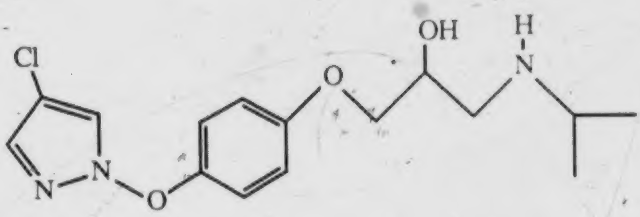
45 (R_2= $CH(CH_3)_2$; R_3= H)

R_1	NAME
a) CH_3CONH	Practolol[272]
b) H_2NCOCH_2	Atenolol[277]
c) $c\text{-}C_3H_5CH_2OCH_2CH_2$	Betaxolol[278]
d) $CH_3OCH_2CH_2$	Metoprolol[279]
e) $CH_3OCH_2CH_2O$	H87/07[280]
f) $CH_3O_2CNHCH_2CH_2$	Pamatolol[281]
g) $(CH_3)_2CHO(CH_2)_2OCH_2$	Bisoprolol[282]



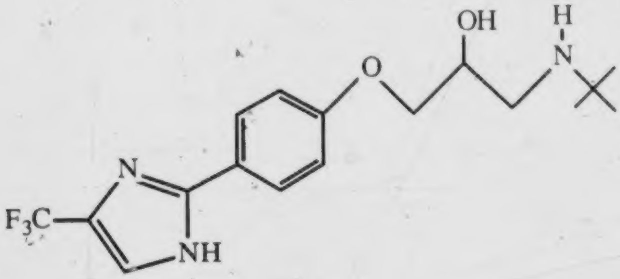
46

The replacement of the *para*-acetamido substituent in practolol (**45a**) by the heterocyclic ring shown in compound (**47**) provided a high cardioselectivity ratio (β_1/β_2 = 100/1)[284].



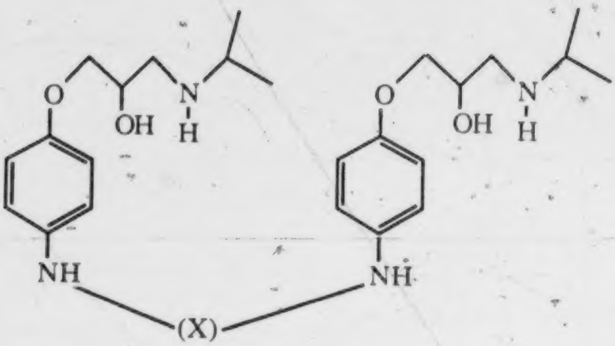
47

The interesting compound (**48**)[285] exhibits a direct vasodilating effect in addition to its β-blocker action. Although compound (**48**) is structurally similar to compound (**47**) it does not possess β_1/β_2 cardioselectivity.



48

A potentiation of β-blocker activity could theoretically occur when a multifunctional drug is able to span several binding sites, but these types of compounds were found to exhibit low potency[286]. In order to increase receptor affinity for β-blockers, the concept of bivalent ligands based on the structure of practolol (**45a**) was employed[287,288] to make binary phenoxypropanolamines (**49**) that exhibited potent and β-cardioselective blockade[289].

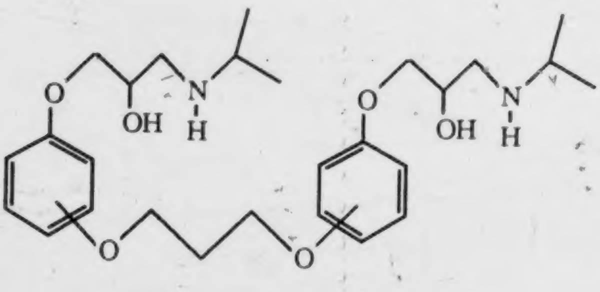


49

X= $-OC-(CH_2)_n-CO-$

X= $-OC-CH_2-NH-(CH_2)_2-NH-CH_2-CO-$

Another series of binary aryloxypropanolamines (**50**) linked through the 2,2'; 3,3'; and 4,4' positions of the aromatic rings of the pharmacophores indicated that the 2,2' compounds tend to be selective β_2-adrenergic blocking agents, the 4,4' binaries tend to be potent and selective β_1-blocking agents, and those compounds with 3,3' linkages exhibit intermediate selectivities[290]. The binary *ortho*-substituted aryloxypropanolamine nebivolol (**51**) is also a chemically novel, potent, and selective β_1-adrenergic antagonist[291].



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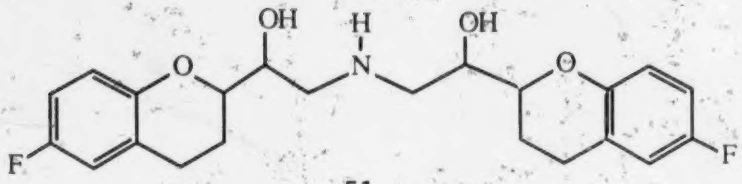
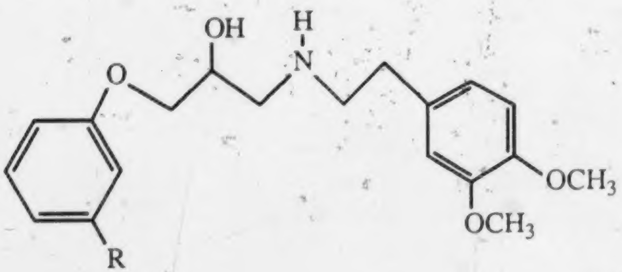


51

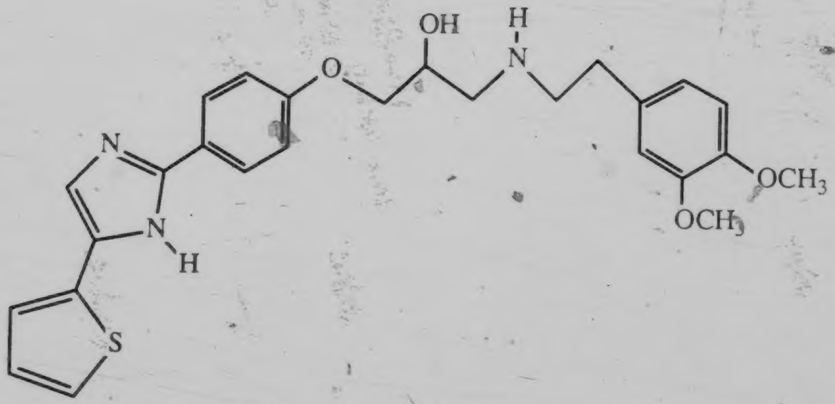
Although cardioselectivity has been shown to be associated with a variety of *para*-substituents in the aryl moiety of class B aryloxypropanolamines,[292,293,294] it also appears to be associated with a low pKa value for the side chain amine nitrogen[295]. More recent investigations have shown that cardioselectivity can also be obtained by replacing a conventional N-isopropyl or t-butyl substituent in the β-blocker by aminoethyl,[296] phenoxy alkylamine,[297] or 3,4-dimethoxyphenethyl substituents[298]. Bevantolol(**52**)[299,300] and HOE 224 (**53**)[301] which have a N-(3,4-dimethoxyphenethyl) substituent, exhibit potent β-blocking activity and high cardioselectivity.



52 R= CH_3, Bevantolol

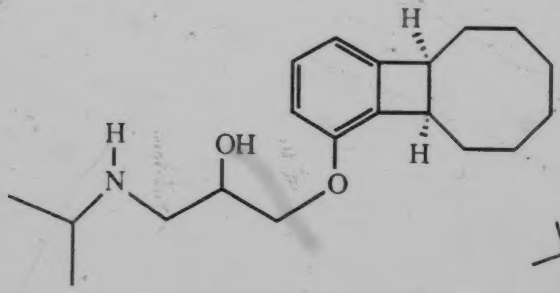
53 R= CH=CH-CN, HOE 224, (β_1/β_2>4000/1)

Further modification of (**52**) and (**53**) at *para*-position gave a highly cardioselective compound (**54**) that displayed about a 9000-fold greater affinity for β_1- relative to β_2-adrenergic receptors[301,302,303].

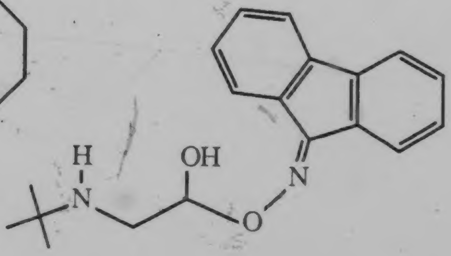


54

Replacement of the phenyl ring in class B aryloxypropanolamines by tricyclic ring system provided compound (**55**) that exhibited a greater β_2-selectivity than propranolol[304,305]. The oxime derivative of 9-fluorenone, IPS-339 (**56**);[306,307,308,309] exhibited significant β-blocking action with preferential action at β_2-receptors.

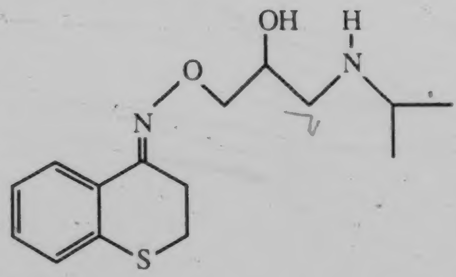


55



56

These results provided a new lead for the design of β_2-selective blocking agents, since oxime derivatives possessing smaller rings such as (**57**)[310] and (**58**)[311] had been reported to exhibit non-selective β-blocking action.



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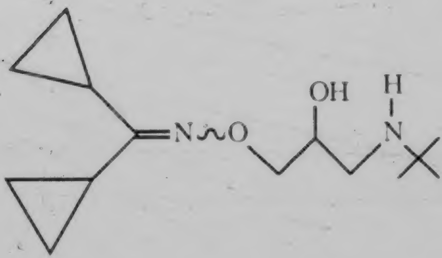
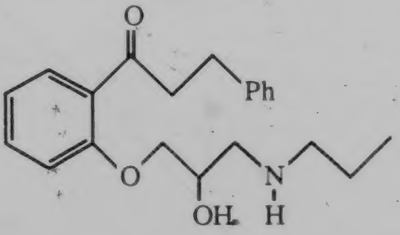


58

Other studies to develop more selective β-blockers have provided a variety of potent class B β-blockers such as propafenone (**59**),[312] diprafenone (**60**),[312] OF-4452 (**61**)[313] and nicainoprol (**62**)[314].



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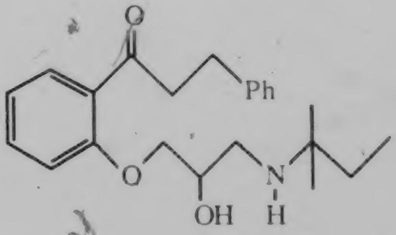

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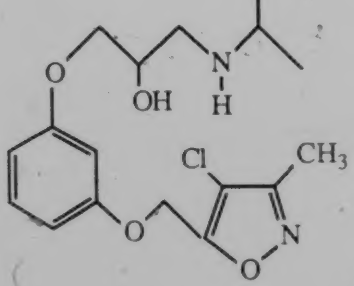

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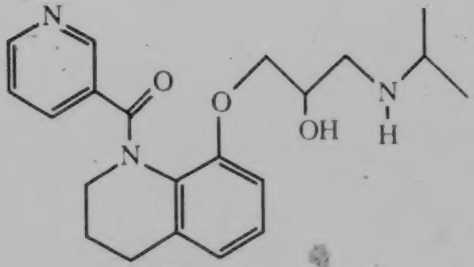
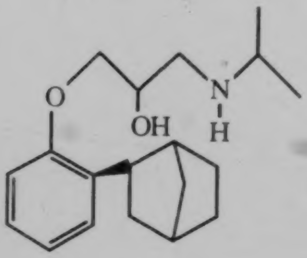


62

Reports continue to appear describing structurally novel agents that exhibit unique pharmacological properties such as the long duration of action observed with FM 24 (**63**)[315], N 696 (**64**)[316] and tertatolol (**65**)[317]. Compound (**66**)[318] and flavodilol (**67**)[319] represent an interesting new class of neuronal catecholamine depleting agents of the diphenylchromonoxy and monophenylchromonoxy propanolamine types. Although, (**66**) and (**67**) clearly fall within the β-adrenoceptor antagonist structural class and exhibited marked antihypertensive activity, they did not possess significant β-adrenoceptor antagonism that was manifested, by a reduction of peripheral noradrenergic stores.



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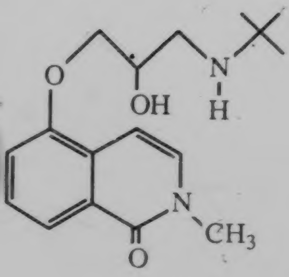

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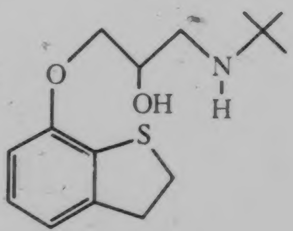
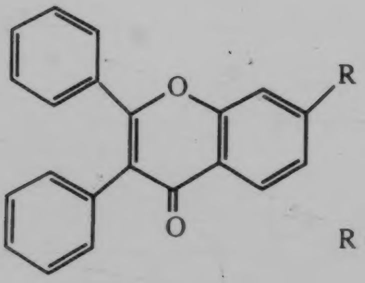


65



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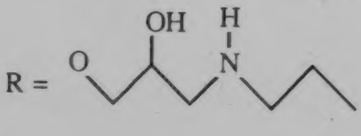
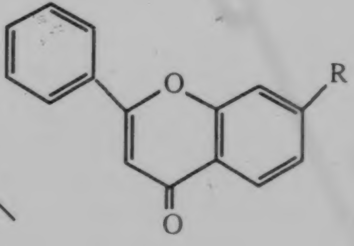
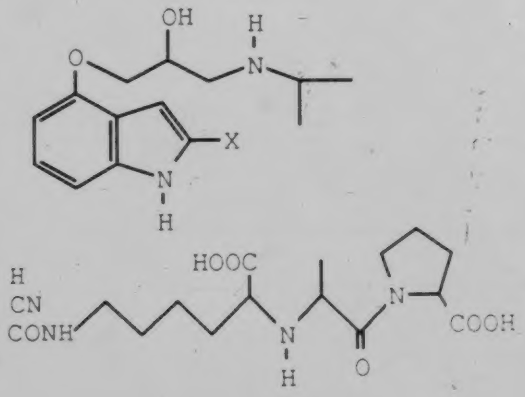




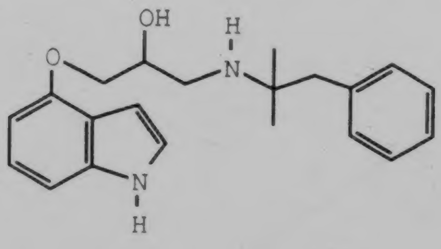
67

Some β-blocking drugs exhibit partial agonist activity, also known as intrinsic sympathomimetic activity (ISA), that is demonstrable in the absence of, or at very low levels of, prior stimulation of the β-receptor. These drugs can either block or stimulate the receptor. One of the most potent β-blocking drugs with partial agonist activity pindolol (**68a**)[320]. Extensive clinical studies with pindolol have shown that it was effective in reducing blood pressure with only a slight or clinically insignificant reduction in pulse rate[321]. Although concommitant agonist activity would minimize adverse effects associated with β-blockade such as precipitation of bronchospasm, augmentation of heart failure, and coldness of the extremities in cold weather, the beneficial aspect have not been substantiated by clinical trials of agents possessing partial agonist activity[322]. The structure-activity relationships for pindolol have been studied extensively by introduction of various substituents at the 2-indolyl ring position to give mepindolol,[254,323] (in Figure 8) and 2-cyanopindolol (**68b**);[324] which have been shown to lower the blood pressure. BWA575C (**69**)[325] is a novel antihypertensive agent that displays angiotensin converting enzyme (ACE) and β-adrenoceptor blocking properties.



68a, X= H
68b, X= CN
69, X= CONH

Replacement of the isopropylamino side chain of pindolol (**68a**) by other bulky alkylamino groups resulted in the syntheses of benzpindolol (**70**),[326] that exhibited antihypertensive and vasodilator activity, and (**71**)[327] that was found to be a potent irreversible β-blocker lacking agonist activity. Bopindolol (**72**), a derivative of mepindolol in which the secondary hydroxyl group of the aliphatic side chain is esterified, was effective in reducing blood pressure without pronounced bradycardia[328]. Replacement of the secondary amine moiety of pindolol by a N^4-diphenylmethylpiperazinyl moiety afforded DPI 201-106 (**73**) which is a positive inotropic agent[329].



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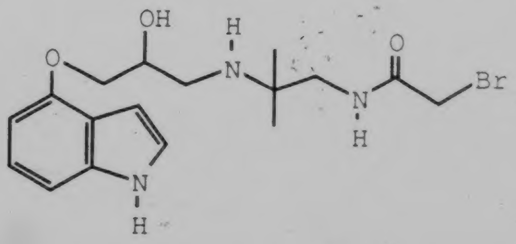

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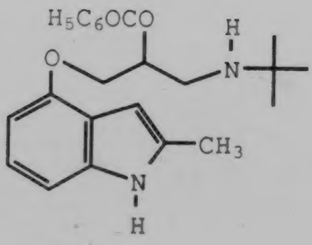

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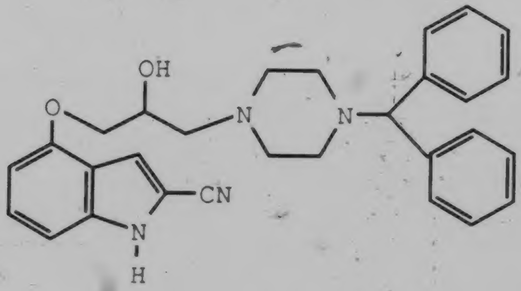
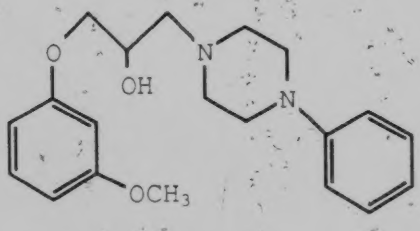


73

Related compounds, in which the amino groups of class B aryloxypropanolamines were replaced by a N^4-arylpiperazinyl moiety provided a large number of active compounds with a broad spectrum of biological activities. For example, 1-(*m*-methoxyphenoxy)-3-(N^4-phenylpiperazinyl)propan-2-ol (**74**)^{330} exhibited hypotensive activity due to ganglionic blockade, 1-(*p*-chlorophenoxy)-3-[N^4-(3,4-dimethoxyphenyl)-piperazinyl]propanol (**75**)^{330} displayed anticonvulsant activity, 1-phenoxy-3-[N^4-(o-tolylpiperazinyl)propan-2-ol (**76**)^{330} acted as an adrenoceptor blocker and 1-phenoxy-3-[N^4-(3,4-dimethoxyphenyl)-piperazinyl]propan-2-ol (**77**)^{330} exhibited hypotensive activity. These studies indicate that biological activity can be modulated by elaboration of either the aryloxy component or the amine moiety.



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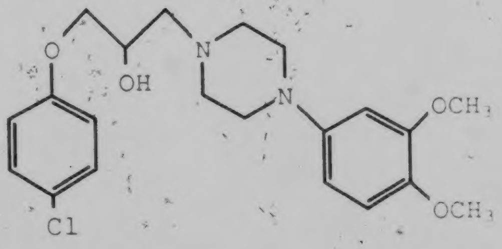

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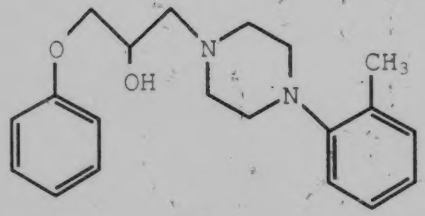

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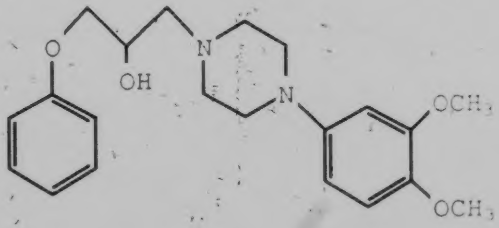
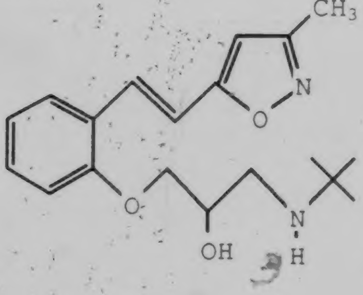


77

1.6.6.0.0 STRUCTURE-ACTIVITY RELATIONSHIPS FOR ARYLOXYPROPANOLAMINE, β-ADRENERGIC BLOCKING AGENTS CLASS B.

It has been suggested that the "combined action" blockade of both β- and α-receptors, which is the case for labetalol (class A), offers an advantage over conventional β-blockers for the treatment of hypertension[331]. The addition of a 2-isoxazolethenyl moiety onto the phenoxypropanolamine moiety (class B) introduces an α-blockade effect to yield (**78**) which is a more potent α,β-adrenoceptor antagonist and antihypertensive agent than labetalol[332]. Other products which possess combined α-, and β-adrenoceptor blocking properties include arotinolol (**79**)[333] and adimolol (**80**)[334].



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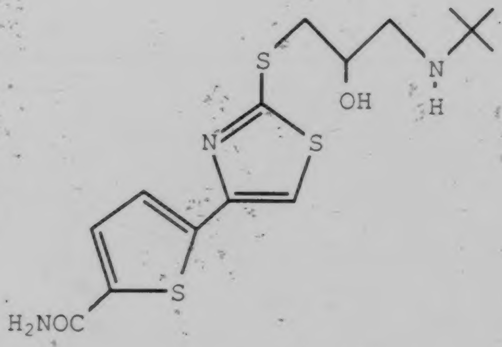

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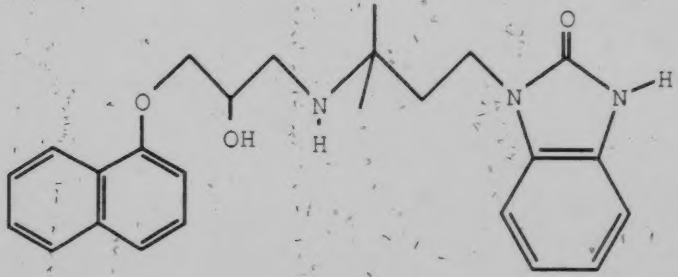
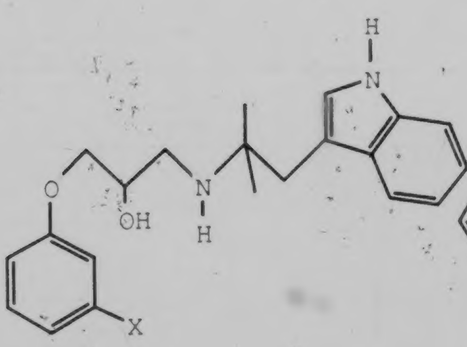
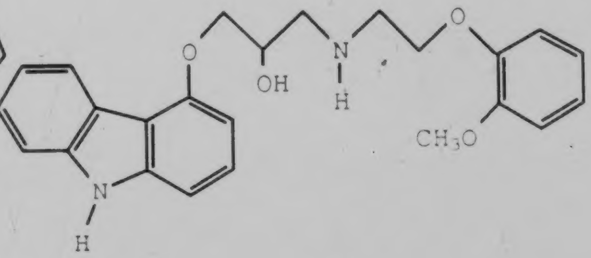


80

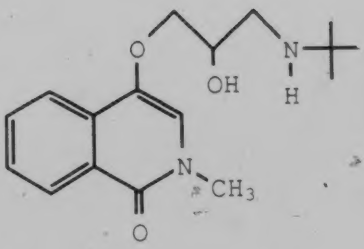
The use of β-adrenoceptor antagonists (β-blockers) for the treatment of essential hypertension is effective in only about 50% of hypertensive patients. Clinically it has been shown that addition of a vasodilator to β-blocker therapy tends to increase the controlled population to about 70%[335]. Compounds possessing both β-blocking action and vasodilator activity have been developed with the primary goal of attenuating the tachycardia associated with vasodilator therapy[336]. Several reports describe compounds that combine β-blocking and vasodilating activity in a single molecule[336,337-343]. Some of these compounds include (**81**),[340] carvedilol (**82**),[344] N-696 (**83**)[345] and SKF-95018 (**84**)[346].



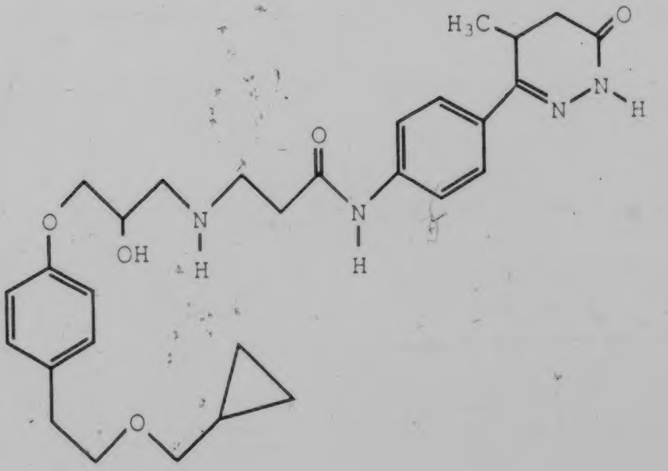
81, X= CH_3, CF_3, CN, $CONH_2$


O
OH
N
H
O
CH_3O
N
H

82

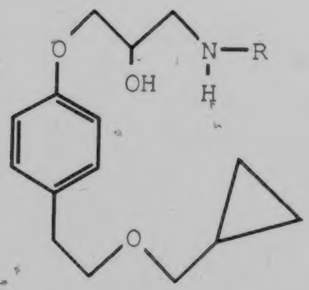

O
OH
N
H
N
CH_3
O

83

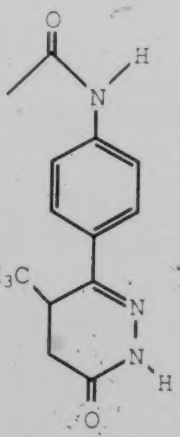

H_3C
O
N
N
H
O
O
OH
N
H
N
H
O

84

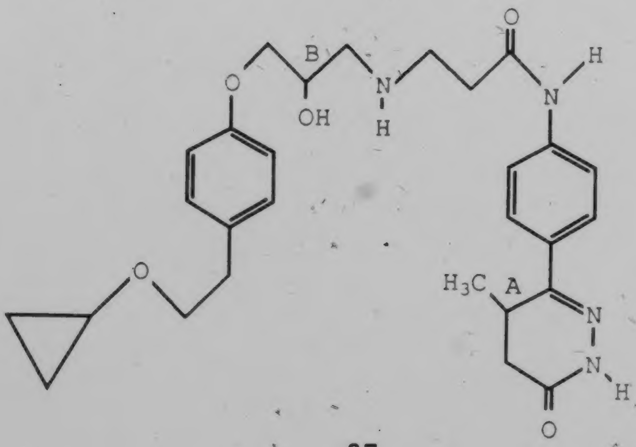
An alternative approach to the design of novel antihypertensive agents with combined vasodilator and β-adrenoceptor antagonist activity involves the joining of an aryloxypropanolamine side chain (**85**) via a spacer link to the amide moiety of the potent vasodilator (**86**)[347] to give (**87**). The R_A,S_B diastereomer of (**87**) is the most active[348].



85

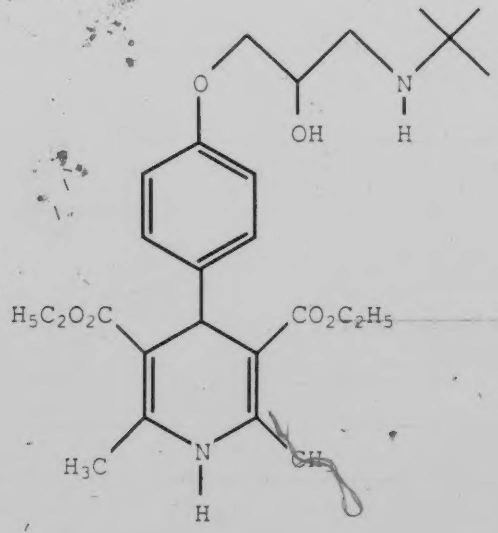

O
H
N
H₃C
N
N
H
O

86


O
B
O
H
N
OH
N
H
H₃C
A
N
N
H
O
O

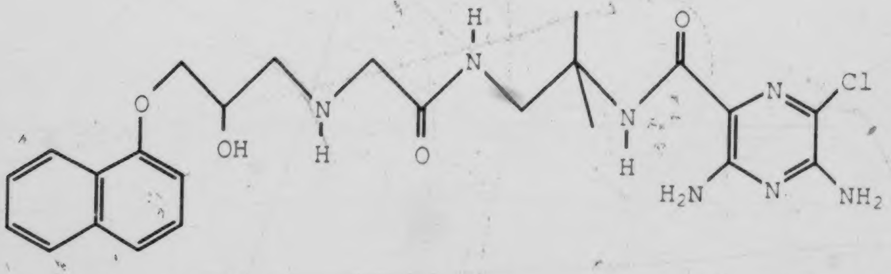
87

The combination of a calcium channel antagonist with a β-adrenergic blocking agent structure[349] for the treatment of severe hypertension has been reported[350]. Structural hybrids of the dihydropyridine class of compounds having an oxypropanolamine moiety capable of inducing β-adrenergic antagonist activity have been prepared (**88**). However, vasodilation does not appear to be the mechanism for its antihypertensive effect[351].



88

Diuretic drugs are used extensively to treat hypertension. Attempts to combine diuretic activity and β-adrenergic antagonism into a single molecular entity have been unsuccessful[352]. However, recently ICI-147,798 (**89**)[353] was found to exhibit both diuretic and β-blocker activity.



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1.6.7.0.0 STEREOSELECTIVITY OF β-ADRENERGIC BLOCKING AGENTS.

The ethanolamine side chain of β-adrenoceptor agonists and antagonists possesses a chiral β-carbon atom. The (-)-(S) or (-)-(R)-configuration[254] seems to be a prerequisite for proper binding to the β-receptor. The absolute configurations of the (-) enantiomers have been established to be "R" for class A, and "S" for class B compounds[355]. The stereoselectivity of β-blockers has been reviewed in considerable detail recently[356]. The activity of racemic β-blockers is attributed mainly to the S(-)-enantiomer[348,357].

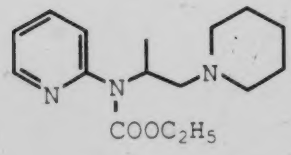
1.7.0.0.0 PHARMACOLOGICALLY ACTIVE PYRIDINES AND REDUCED PYRIDINES.

The pharmacological activity of pyridines and reduced pyridines has been reviewed[358,359].

1.7.1.0.0 PYRIDINES.

Compounds containing a pyridine ring and derivatives thereof exhibit a wide spectrum of pharmacological activities. Some of these include analgesic (**90**)[360], antiarrhythmic (**91**)[361], antiinflammatory (**92**)[362], antimalarial (**93**)[363], vasodilator (**94**)[364], (**95**)[365,366] and

(96)[367,368], vitamine **(97,98,99)**[369], hypotensive **(100)**[370] and **(101)**[371], anticonvulsant **(102)**[372] and antipicornavirus agents **(103)**[373] The pyridyl compound FR 46171 (**104**), has been used for the treatment of angina[374,375].



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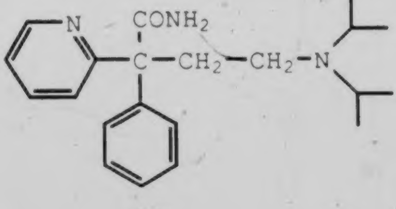

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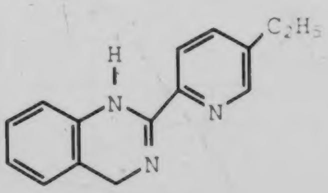

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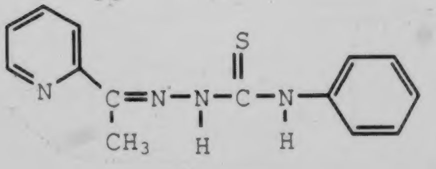

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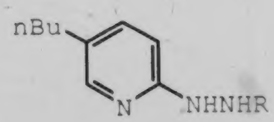

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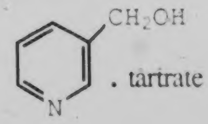

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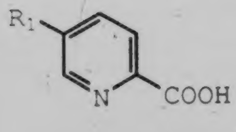
R= H, $COCH_2CH_2CH(NHAc)COOH$



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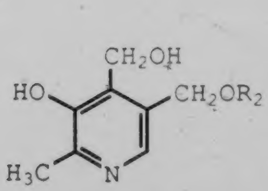

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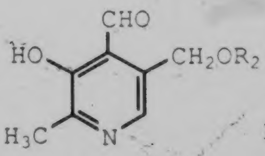

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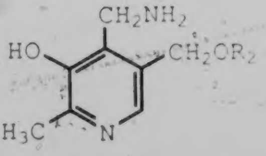
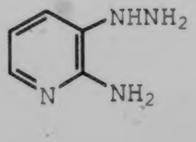


99

R_1= a) $4HO–C_6H_4–CH_2$
- b) n-Bu
- c) 4-Cl-Bu

R_2= a) H
- b) $PO(OH)_2$



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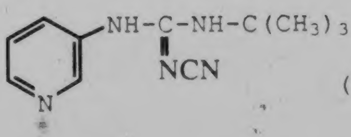

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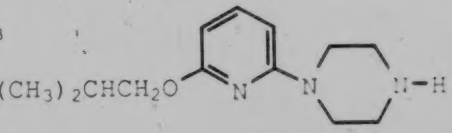

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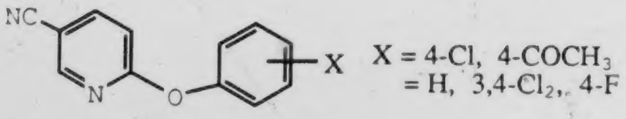
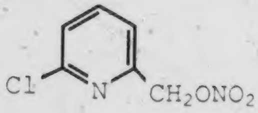
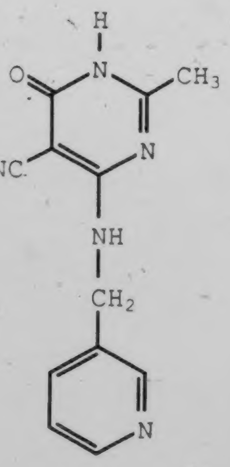

NC
N
O
X
X = 4-Cl, 4-COCH$_3$
= H, 3,4-Cl$_2$, 4-F

103

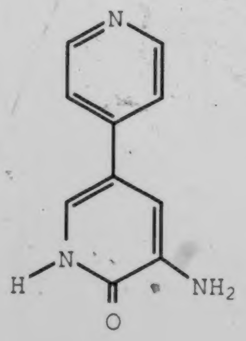

Cl
N
CH$_2$ONO$_2$

104

The recent discovery of a new class of nonglycoside and noncatecholamine inotropic agents culminated in the development of (**105**),[376] amrinone (**106**) and milrinone (**107**)[377] that are used in the treatment of congestive heart failure.


H
O
N
CH$_3$
N
NC
NH
CH$_2$
N

105



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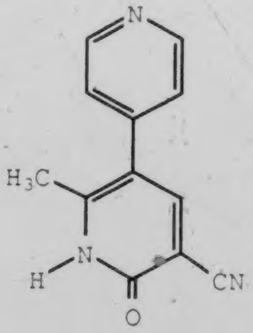
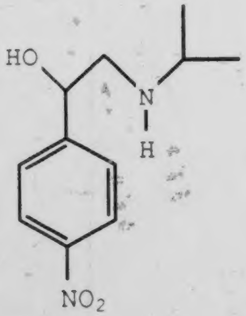


107

1.7.2.0.0 PYRIDINE AND NITROBENZENE BIOISOSTERISM.

Bioisosteres are defined as groups or molecules which possess similar chemical and physical properties that induce similar biological effects[378]. Application and example of bioisosterism in drug design has been reviewed recently[379]. Although the pyridyl and nitrobenzene ring are bioisosteres that have similar electron density distributions at similar positions, in some instances pyridyl compounds have been found to display better pharmacological profiles. For example, the pyridine isostere (**109**) of INPEA (2-(*p*-nitrophenyl)-1-isopropylamino-2-ethanol) (**108**) was found to act as both a partial β-agonist and a partial β-antagonist in isolated guinea pig atrial strips against isoproterenol challenge. On the other hand, the 4-pyridyloxypropanolamine (**110**) (class B) derivative of (**109**) (class A) was a pure antagonist (pA_2 = 7) that was 10 times as potent as its *p*-nitrophenoxy isostere[380]. Many substituted pyridines possess vasodilator activity[364-368]. A combination of vasodilator and β-adrenergic blocker activities for some pyridine-containing compounds such as SC-36859 (**111**)[381] and (S)-2-[3-(*tert*-butylamino)-2-hydroxy propoxy]-3-cyanopyridine (**112**)[382] have been reported.



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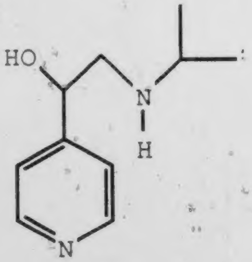

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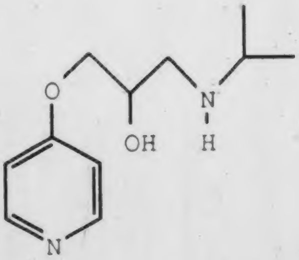

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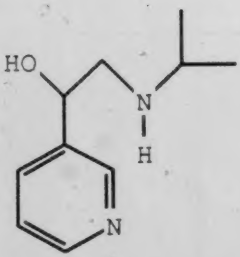

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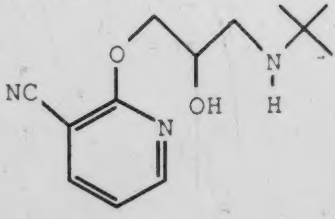
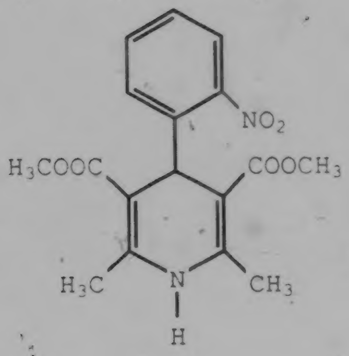


112

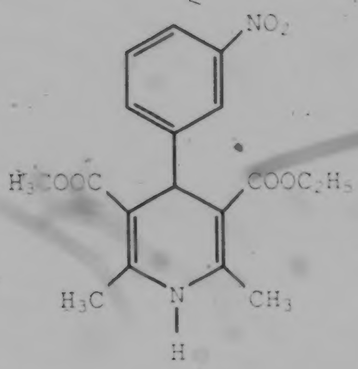
There are three positional isomers for compounds containing a pyridyl ring substituent (2-, 3- or 4-pyridyl) that may exhibit a variety of pharmacological activities. For example, replacement of the 4-(2-nitrophenyl) substituent present in nifedipine (**113**) by a 4-(pyridyl) ring afforded calcium channel antagonist. Compounds where the relative potency profile was 2-pyridyl> 3-pyridyl> 4-pyridinyl^{383,384}. A study in this research group also showed that the point of attachment of a pyridyl ring was a determinant of histamine H_2-receptor antagonist activity where the potency order was 2- > 4- > 3-pyridinyl^{385}.

1.7.3.0.0 PHARMACOLOGICAL APPLICATIONS OF REDUCED PYRIDINES.

Since the discovery of 1,4-dihydropyridines (DHPs) by Hantzsch more than a 100 years ago^{386}, many DHP derivatives^{387} have attained considerable importance as coenzymes in dehydrogenases (NAD(P)H)^{388}, as intermediates in alkaloid synthesis,^{389} and as biological agents with a spectrum of biological activities^{387}. DHPs with calcium channel antagonist activity are useful drugs^{390}. The most potent and most specific calcium channel antagonists belong to the 1,4-dihydropyridine class which is represented by symmetrical nifedipine (**113**)^{391} and unsymmetrical nitrendipine (**114**)^{392}. Nifedipine has proved to be clinically effective for the treatment of cardiovascular diseases including angina^{393,394} and hypertension^{395,396}. The high lipophilicity and the ease of aromatization of prodrug dihydropyridines to pyridinum salts has been used to deliver acetylcholinesterase reactivator drugs to the brain$^{397,398-401}$. This concept has also been used to enhance the delivery of amines, catecholamines, and steroids to the brain^{398,401,402}.

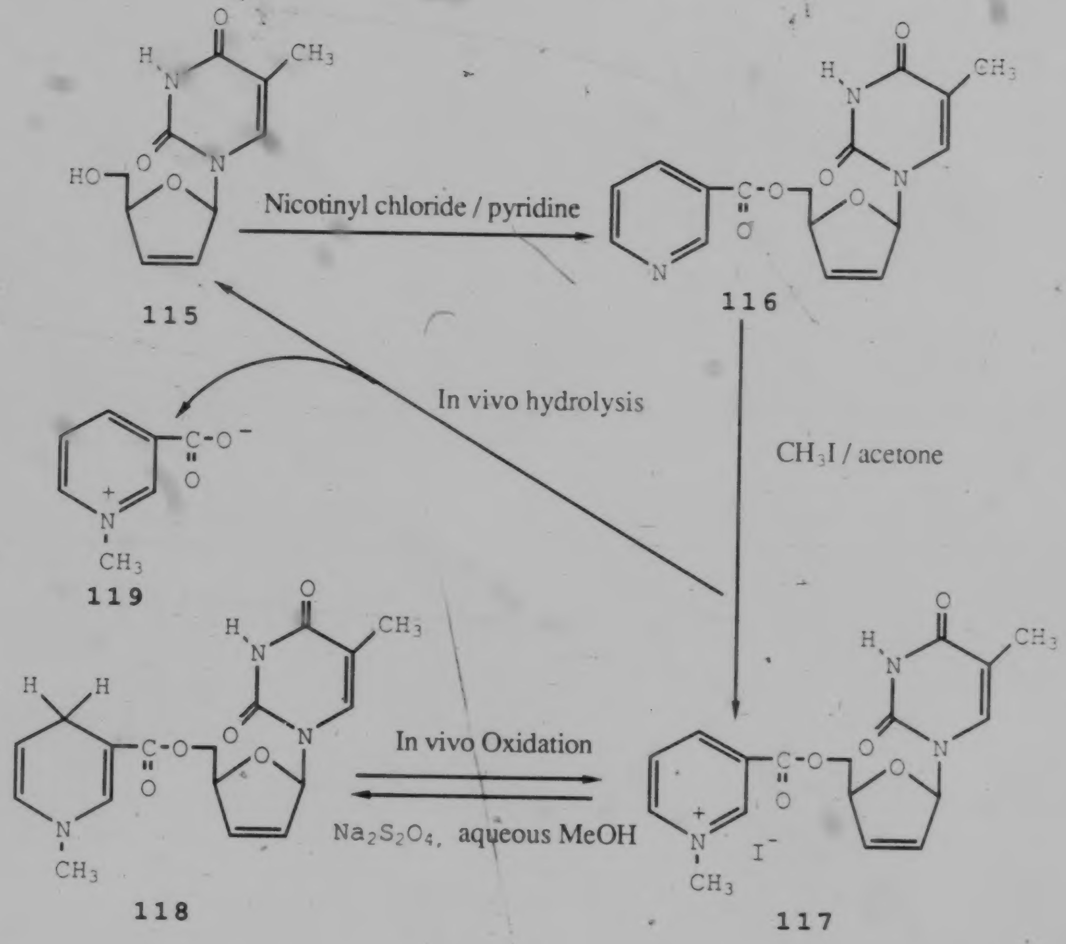


113

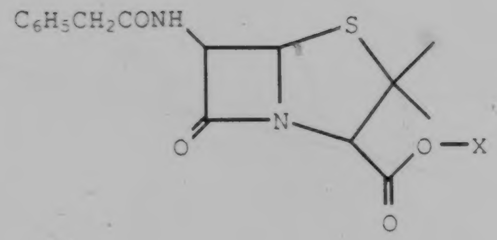


114

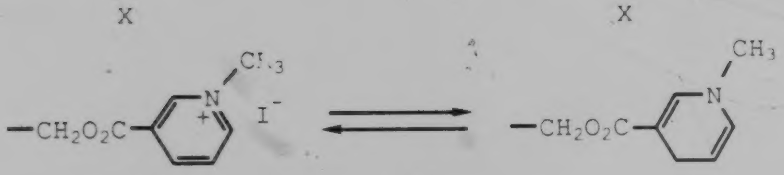
In recent years, a new concept of a brain-specific drug delivery system has been developed that is based on a redox system analogous to the endogenous NADH $\rightleftharpoons$ NAD$^+$ coenzyme system[397,398,400]. The utility of the dihydropyridine $\rightleftharpoons$ pyridinium salt redox system for the specific delivery and sustained local release of anti-AIDS (acquired immunodeficiency syndrome) antiviral nucleosides (**115**) via a chemical delivery system (**118**) (see Scheme 1) to the brain of mice has prompted a potentially useful approach for the treatment of AIDS dementia complex[403]. Success is also being achieved by using this redox system to deliver polar β-lactam antibiotics as benzyl penicillin (**120**)[404,405] to the brain for the treatment of cephalic infections. An extensive bibliography describing the biology and chemistry of dihydropyridines has been published[406,407].


115
Nicotinyl chloride / pyridine
116
In vivo hydrolysis
CH3I / acetone
119
118
In vivo Oxidation
Na2S2O4, aqueous MeOH
117

Scheme 1. The dihydropyridine ⇌ pyridinium salt redox system for cephalic delivery of an anti-AIDS nucleoside (**115**).



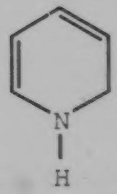
X = H, Benzylpeniciline, BP



120

1.7.4.0.0 THE CHEMISTRY OF DIHYDROPYRIDINES.

The synthesis, physical and chemical properties and reactions of dihydropyridines have been reviewed[407-410]. There are five possible isomeric dihydropyridines; 1,2-(**121**), 1,4-(**122**), 2,3-(**123**), 3,4-(**124**), and 2,5-(**125**).



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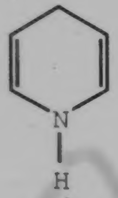

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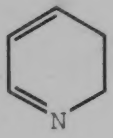

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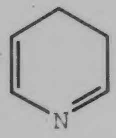

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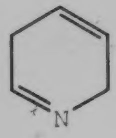


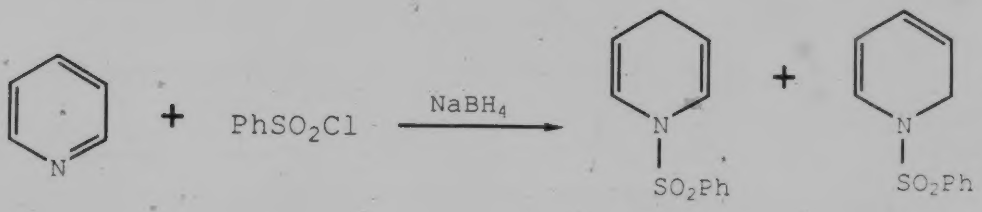
125

All these isomers are very unstable since they decompose rapidly in air[411]. The majority of dihydropyridines are of the 1,2-, and 1,4 types, since these have a more extensively conjugated π electron system than the others. Electron-withdrawing substituents, such as COOH, $COCH_3$, $CONH_2$, CO_2CH_3, CN, NO_2 and oxazolin-2-yl at the C-4 and/or C-5 position stabilize dihydropyridines by extending the conjugation [illegible]. In [illegible] electron donating substituents at these same positions exert a destabilizing effect[412f].

1.7.4.1.0 SYNTHESIS OF DIHYDROPYRIDINES.

1.7.4.1.1 SYNTHESIS OF DIHYDROPYRIDINES BY REDUCTION OF PYRIDINES AND PYRIDINIUM SALTS.

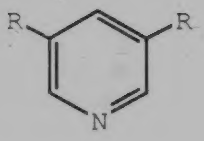
The synthesis of dihydropyridines by the reduction of pyridines or pyridinium salts with complex metal hydrides[413,412f] is often complicated by the formation of isomeric mixtures of 1,2-, 1,4- and /or 1,6-dihydropyridines as well as tetrahydropyridines[414]. Knaus et al[415] found that the reaction of benzenesulfonyl chloride (**126**) with pyridine (**127**) (as both solvent and reactant) in the presence of sodium borohydride at 25 °C afforded a 5:4 ratio of 1,4 (**128**) to 1,2 (**129**) isomers whereas at -65 °C the ratio was 1:8.

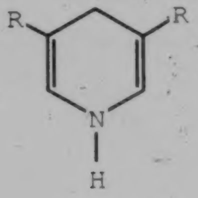


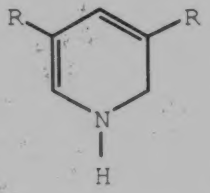
127 **126** **128** **129**

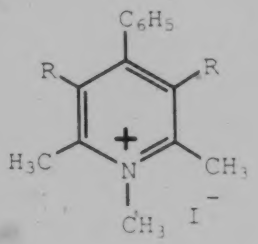
	128		129
25 °C	5	:	4
-65 °C	1	:	8

The isomeric dihydropyridine product ratio can also be altered by using different reducing agents such as sodium cyanoborohydride ($NaCNBH_3$)[411]. For example, reduction of pyridine-3,5-dicarboxylate (130) using $NaCNBH_3$ afforded high yields of 1,4-dihydropyridines (131) with only a trace of 1,2-isomer (**132**), whereas reduction using borane afforded only 1,2 isomer (**132**)[411]. Lithium aluminum hydride reduction of (**133**) has been reported to yield a 1,2-dihydropyridine[416]. These observations suggest that the steric effect of the bulky hydride reagent also plays an important role in determining the position of hydride attack.







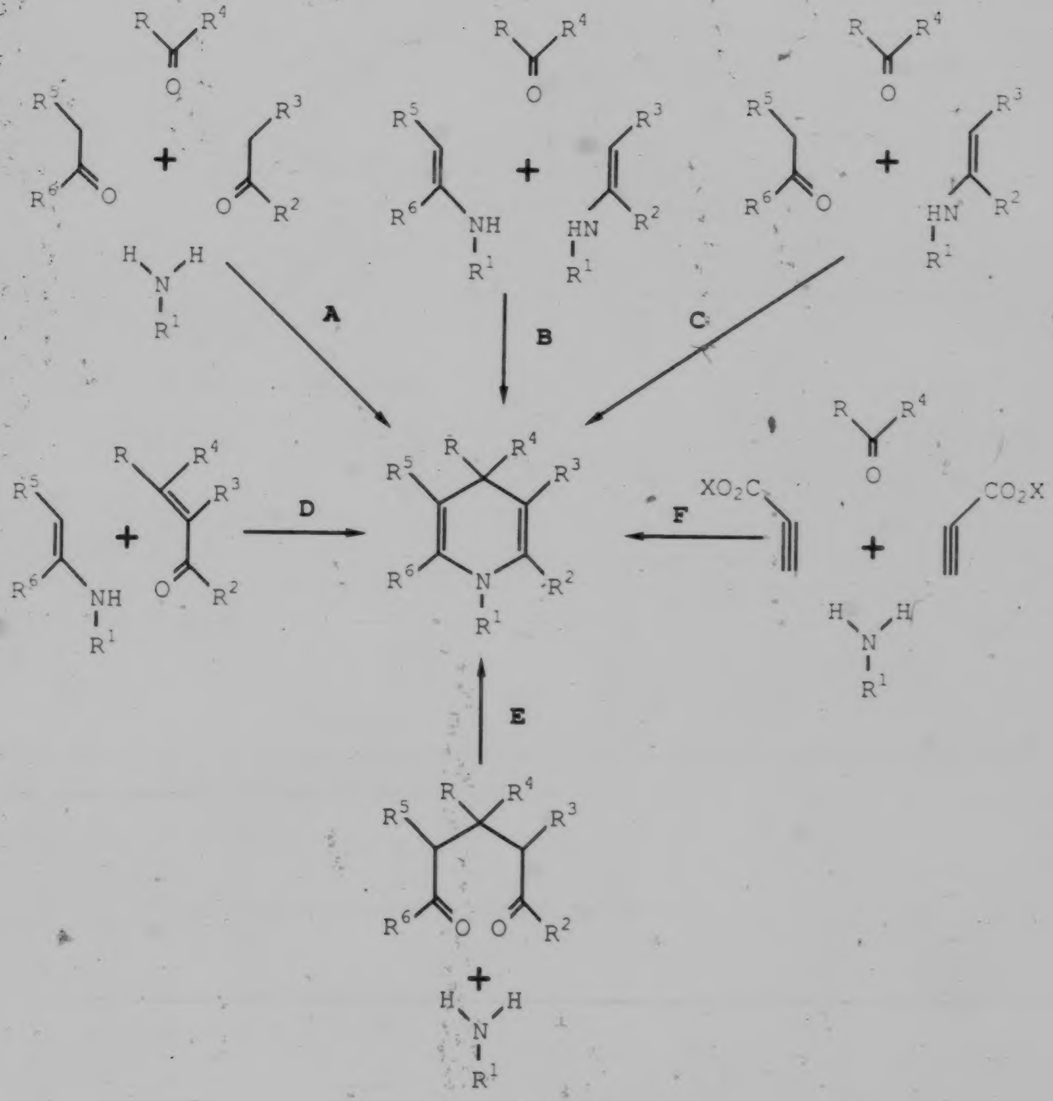


R= COOEt

130 **131** **132** **133**

1.7.4.2.0 SYNTHESIS OF 1,4-DIHYDROPYRIDINE BY CYCLOCONDENSATION REACTIONS.

The Hantzsch synthesis[386] and related cyclocondensations are the main methods used to synthesize 1,4-dihydropyridines. Various modifications of this type of cyclocondensation reactions have been reviewed[406,409,417]. The principal synthetic pathways are outlined in Scheme 2.



Scheme 2. Synthesis of 1,4-dihydropyridines by cyclocondensation reactions.

1.7.4.3.0 SYNTHESIS OF DIHYDROPYRIDINES USING NUCLEOPHILIC ORGANOMETALLIC REAGENTS.

Nucleophilic addition of organometallic reagents to pyridinium salts has provided valuable and convenient methods for the synthesis of 2- and 4-substituted 1,2- and 1,4-dihydropyridines[409,410]. The regioselectivity of these reactions has been found to be dependent upon the properties of the organometallic reagent. Thus 4-substituted-1,4-dihydropyridine derivatives are produced exclusively when organocopper reagents are used[418,419], whereas Grignard,[420-423] and organocadmium reagents[423] have been reported to attack predominantly at the 2-position of pyridinium salts. These results can be explained using the hard and soft character concept (Figure 9)[424] and steric size[425] of nucleophiles. Figure 9 shows on the right the antibonding molecular orbitals of pyridinium ions. The circles represent the $(C_s^n)^2$, the square of the coefficients of the atomic orbitals for positions 2 and 4 which are the two possible reacting centers. On the left side, five nucleophiles of increasing hardness (k_m = -0.3, -0.2, -0.1, 0, 0.1) are represented through their highest filled orbital. For the hard nucleophiles (k_m = 0.1), the most reactive center is position 2, but as the softness of the nucleophile increases (k_m decreases), a progressive change to position 4 occurs. This has been observed for hard nucleophiles such as BH_4^-, aniline, and hydroxide ions which attack position 2, whereas the soft CN^- and $S_2O_4^{-2}$ nucleophiles react at position 4[426]. In the case of 3-substituted pyridines it is highly desirable but not possible to control the regioselectivity of 1,2 and 1,6-addition[425,427-429]. 1,4-Addition is not affected by various 3-substituents[428,429].

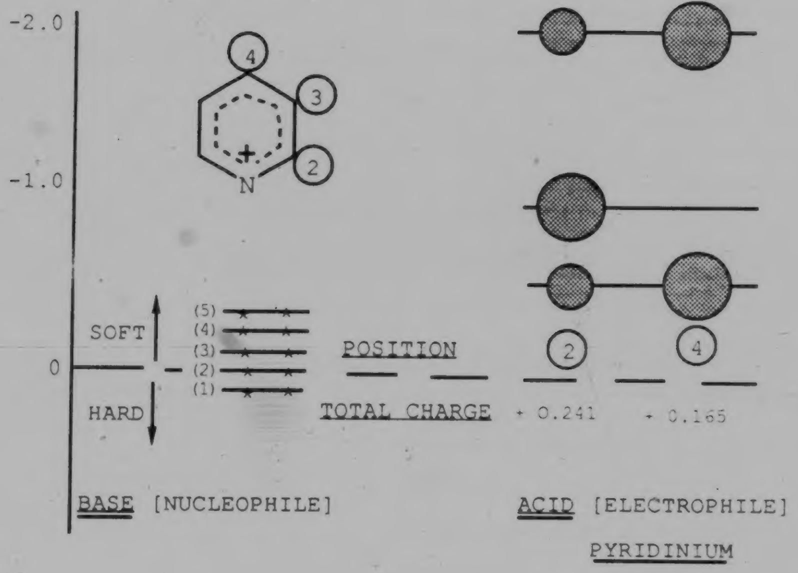
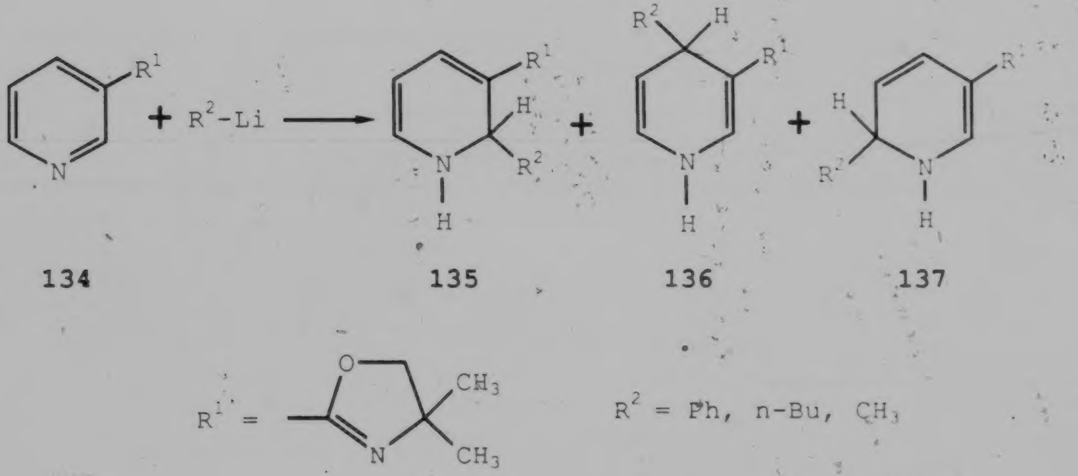

-2.0
-1.0
0
4
3
2
N
+
SOFT
HARD
(5)
(4)
(3)
(2)
(1)
POSITION
TOTAL CHARGE
2
4
+ 0.241
+ 0.165
BASE [NUCLEOPHILE]
ACID [ELECTROPHILE]
PYRIDINIUM

Fig. 9. Schematic representation of the interaction between several nucleophiles and the antibonding orbitals of pyridinum salts.

Knaus and Dubey[430,412a] found that the reaction of 3-(4,4-dimethyloxazolin-2-yl)pyridine (**134**)[431] with nucleophilic organolithium reagents as phenyl-, n-butyl- and methyllithium afforded stabilized N-unsubstituted 1,2-dihydro, 1,4-dihydro and/or 1,6-dihydropyridines (**135-137**). The regiochemistry of the nucleophilic addition reaction was solvent and temperature dependent and upon the nature of the organolithium reagent[430]. Reactions carried out using the less polar ether as solvent, provided higher yields of C-2 (**135**) and C-6 (**137**) substituted products, whereas reactions performed in tetrahydrofuran provided higher yields of C-4 substituted products (**136**). A decrease in reaction temperature, increased the yield of the 1,4-dihydro isomer (**136**) in both solvents. Reactions employing phenyllithium were [illegible] regioselective than those utilizing n-butyl- or methyllithium since the former reagent afforded only 1,2- (**135**) and 1,4- (**136**) dihydro products, whereas the latter reagent yielded all three isomeric products (**135-137**).



134 **135** **136** **137**

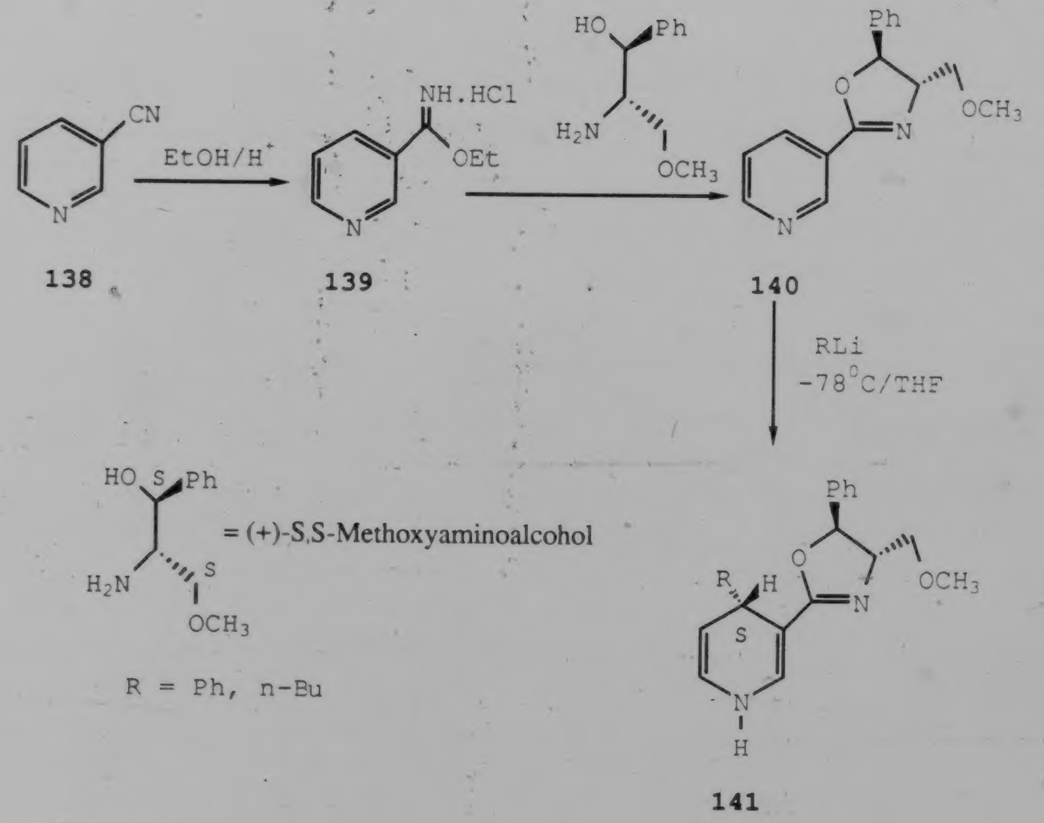
R^1 =

R^2 = Ph, n-Bu, CH_3

Several other regioselective methods have been developed for the sythesis of 1,2-dihydro,$^{432-436}$ and 1,4-dihydropyridines^{437,438}.

1.7.4.4.0 SYNTHESIS OF CHIRAL 1,4-DIHYDROPYRIDINES.

Unsymmetrical 4-aryl-1,4-dihydropyridines such as nitrendipine (**114**) possess a chiral atom at C-4 and therefore exist as a mixture of two enantiomers that exhibit biologically different actions (Ca^{2+} antagonist and Ca^{2+} agonist)^{439}. Thus, enantioselective syntheses of chiral 4-aryl-1,4-dihydropyridines are highly desirable. Some chiral synthetic methods have been developed$^{440-443}$, one of which is outlined in scheme 3$^{441-443}$.


CN
EtOH/H$^+$
NH.HCl
OEt
HO
Ph
H_2N
OCH_3
O
N
RLi
-78°C/THF
138
139
140
141
HO S Ph
= (+)-S,S-Methoxyaminoalcohol
S
R = Ph, n-Bu
R H
S
N
H

Scheme 3. Synthesis of chiral 1,4-dihydropyridines.

2.0.0.0 0 OBJECTIVES OF RESEARCH.

Cardiac diseases and vascular disorders are two of the primary causes of death today. Calcium channel and β-adrenoreceptor antagonist drugs have been successfully used to treat some of these disorders. β-Adrenoreceptors play an important function in the regulation of the autonomic nervous system. β-Adrenoreceptor blocking drugs were originally developed as a treatment for angina pectoris. Their efficacy as antihypertensive agents was discovered as a result of observations made during angina clinical trials. In addition, β-adrenoreceptor blocking drugs are useful therapeutic agents for the treatment of arrhythmias,[104] myocardial infarction,[106] thyrotoxicosis,[107] glaucoma,[108] and migraine headache[109]. Dichloroisoproterenol was the first nonselective β-adrenoreceptor antagonist discovered. Subsequently, many potent β-adrenoreceptor antagonists were synthesized which belong to two general classes, viz class A phenylethanolamines and class B aryloxy- propanolamines. These two classes of compounds are structurally similar since they differ only by an OCH_2 spacer in the side chain. The discovery of propranolol, the first clinical β-adrenergic antagonist, stimulated the initiation of many structure-activity studies that subsequently provided a large number of compounds exhibiting greater potency and selectivity. Most structural modifications involved changes in the aromatic ring substituents and more recently, substituents on the basic amino group.

A group of propranolol analogues was therefore synthesized to investigate:

1. The effect which replacement of the aryl or aryloxy moiety by novel heterocyclic [illegible] alkylamino moiety by

different alkylaryl groups had upon β-adrenergic antagonist activity such as:

a. The aryloxy moiety of propranolol was replaced by a 1,2-, 1,4-, or 1,6-dihydropyridine ring system that is stabilized by a single electron-attracting 3-cyano, or 3-(4,4-dimethyloxazolin-2-yl) substituent, or an isoquinolone or quinazolone ring system.

b. The secondary alkylamino moiety of propranolol was replaced by a 1,2-, 1,4-, or 1,6-dihydropyridine ring system.

c. The aryl moiety of propranolol was replaced by a 2-, 4-, or 5-quinolinyl, 2-pyrimidinyl or 5-isoquinolinyl ring system, the N-alkyl substituent of these heterocyclic compounds was replaced by a cyclohexyl, 3-phenyl-1-propyl or 3-indolyl-t-butyl group, and the N-alkylamine moiety was replaced by a piperazinyl moiety.

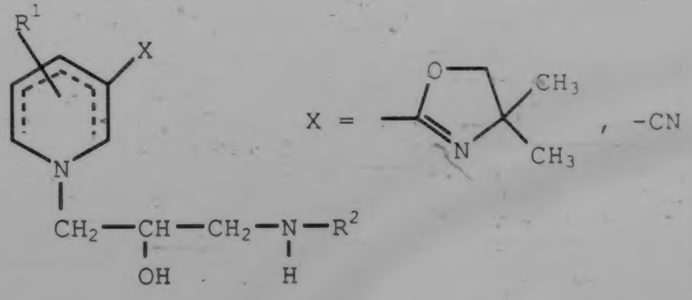
2. The effect of the configuration of the oxypropylamino side chain and the incorporation of a substituent containing a second chiral carbon such as a S-α-methylbenzyl substituent onto the oxypropylamino chain, upon β-adrenergic antagonist activity.

The design, synthesis and pharmacological evaluation of these different classes of structurally related compounds was investigated to develop structure-activity relationships (SARs) with respect to β_1- and β_2-adrenergic antagonist activities.

3.0.0.0 0 RESULTS AND DISCUSSION.

3.1.0.0 0 SYNTHESIS OF 1-{1-[2-, 4- OR 6-ALKYL(PHENYL)-3-SUBSTITUTED)]DIHYDROPYRIDYL}-3-ALKYLAMINO-2-PROPANOLS.

The discovery and clinical success of propranolol (**7**) stimulated the initiation of many structure-activity studies that subsequently provided a large number of compounds having greater potency and selectivity. The replacement of the aryloxy moiety of propranolol by a 1,2-, 1,4- or 1,6-dihydropyridine ring system that is stablized by a single electron-attracting 3-cyano,[444] or 3-(4,4-dimethyloxazolin-2-yl)[430,412a] substituent afforded compounds of general structure (**142**). These studies were initiated to determine the effect which replacement of the naphthyloxy moiety of propranolol by a dihydropyridyl ring system has upon β-adrenergic antagonist activity.



142

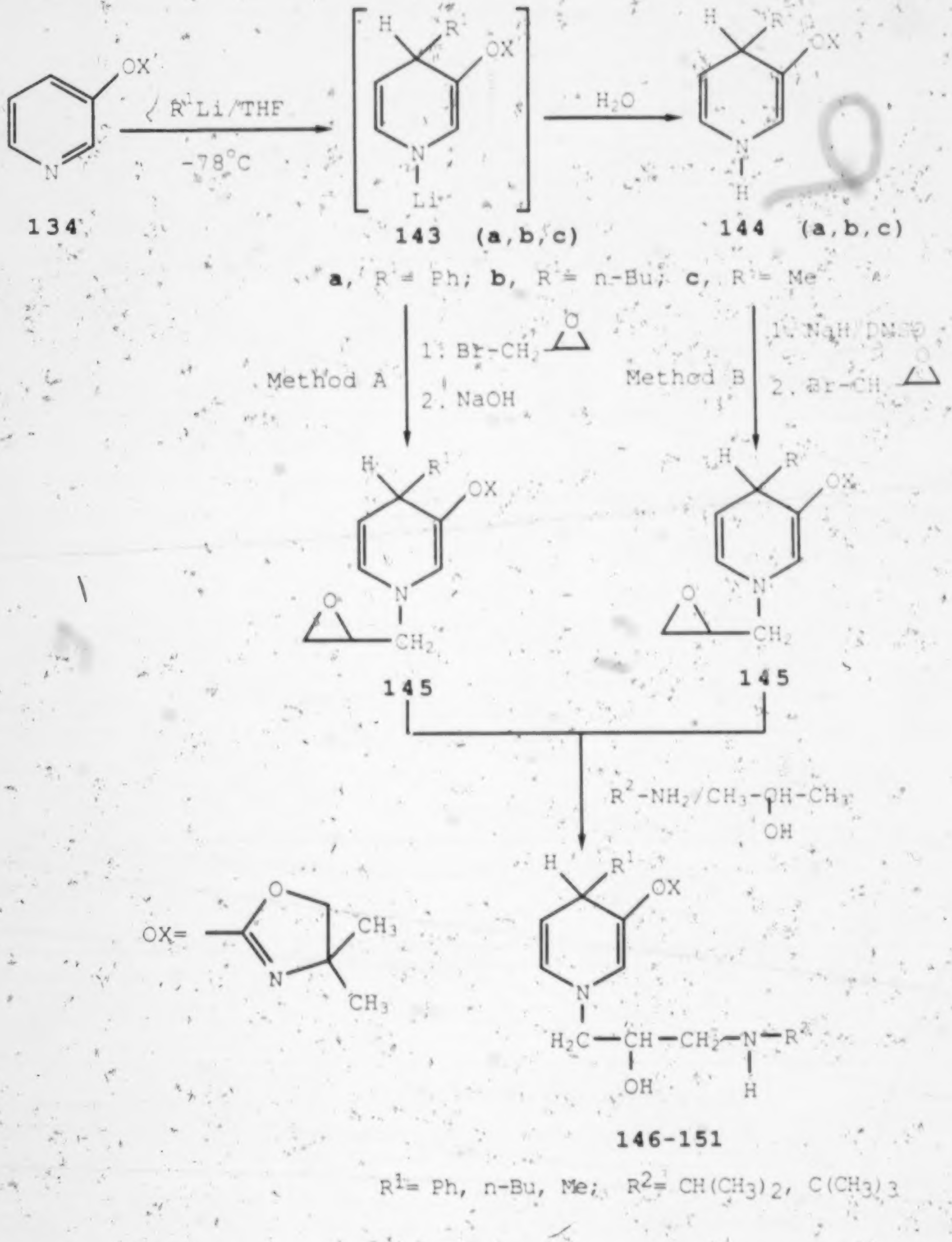
R^1= Ph, n-Bu, t-Bu, Me; R^2= $-CH(CH_3)_2$, $-C(CH_3)_3$

3.1.1.0.0 SYNTHESIS OF 1-{1-[4-ALKYL(ARYL)-3-(4,4-DIMETHYL-OXAZOLIN-2-YL)-1,4-DIHYDROPYRIDYL]}-3-ALKYLAMINO-2-PROPANOLS.

The N-lithio-4-alkyl(aryl)-1,4-dihydropyridines (**143**) were prepared by the reaction of (**134**)[431] with organolithium reagents such as phenyl-, n-butyl- or methylithium in dry tetrahydrofuran under a nitrogen atmosphere at -78 °C. Reaction under these conditions affords predominately (n-BuLi, > 88.5%; MeLi, > 95%) or exclusively (PhLi) (**143 a-c**), respectively. Treatment of (**143**) with 1 equivalent of water yields the respective N-unsubstituted-4-alkyl(aryl)-1,4-dihydropyridines (**144**)[430]. Two synthetic methods (A and B) used for the synthesis of (**146-151**) are outlined in Scheme 4. The direct reaction of (**143**) with epibromohydrin in THF (method A) at -78 °C followed by warming to 25 °C afforded (**145**) in 30-45% yields, whereas reaction of the pure isolated 1,4-dihydropyridines (**144**) with epibromohydrin in DMSO solution in the presence of NaH (method B) at room temperature afforded (**145**) in 60-70% yields. The lower yields obtained using method A are attributed to concomitant reaction of (**143**) with the epoxide ring and to the formation of intractable material. The subsequent reactions of 1-{1-[4-alkyl(aryl)-3-(4,4-dimethyloxazolin-2-yl)]-1,4-dihydropyridyl}-2,3-epoxy-propane (**145**) with alkylamines in 2-propanol afforded (**146-151**). The analytical data for (**146-151**) are summarized in Table 1 and the ^{1}H nmr and ir spectroscopic data are recorded in Table 2. The ^{1}H nmr spectra for compounds (**146-151**), prepared using either method A or B, exhibited dual resonances for the dihydropyridyl H-2, H-6 and H-5 resonances (ratio 1:1) which is attributed to the presence of diastereomers that exhibit different spectra. It is plausible that

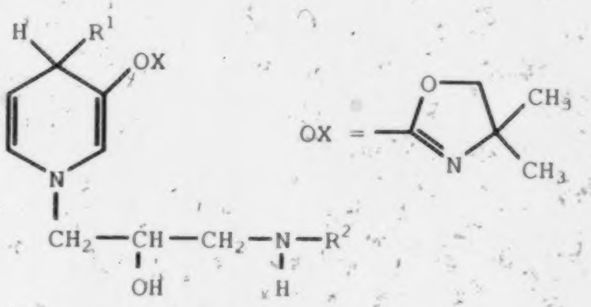
(**146-151**), which possess two chiral centers, exist as a mixture of four diastereomers (SS, RR, SR, RS). The diastereomers could not be separated by thin layer or column chromatography. Interpretation of the mass spectra for 1-{1-[4-alkyl(aryl)-3-(4,4-dimethyloxazolin-2-yl)]-1,4-dihydropyridyl}-3-alkylamino-2-propanols (**146-151**) indicated that the most prominent fragmentation involves the loss of the C-4 group[444]. Less extensive fragmentations include the loss of the N-alkyl substituent, and cleavage of the N-substituted side chain (Path A) for compounds (**148-150**). The other major fragmentation pathway for compounds (**146,147** and **151**) involved the loss of a dihydropyridyl radical (Path B) as illustrated in Scheme 5.

Compound (**146**) undergoes a characteristic major loss of a dihydropyridine radical as indicated by the presence of the base peak at m/z 130.1231 ($C_7H_{16}NO^+$, 100%) shown in Scheme 6 Path A. A less extensive fragmentation is the loss of the C-4 DHP phenyl group shown by the presence of an ion at m/z 306.2190 ($C_{17}H_{28}N_3O_2^+$, 79.9%), as illustrated in Scheme 6 Path B.


134
R'Li/THF
-78°C
143 (a,b,c)
H2O
144 (a,b,c)
a, R = Ph; b, R = n-Bu; c, R = Me
Method A
1. Br-CH2
2. NaOH
Method B
1. NaH DMSO
2. Br-CH2
145
145
R2-NH2/CH3-CH-CH3 OH
146-151
R1= Ph, n-Bu, Me; R2= CH(CH3)2, C(CH3)3
OX=

Scheme 4. Synthetic routes for the preparation of 1-{1-[4-alkyl(aryl)-3-(4,4-dimethyloxazolin-2-yl)]-1,4-dihydropyridyl}-3-alkylamino-2-propanols.

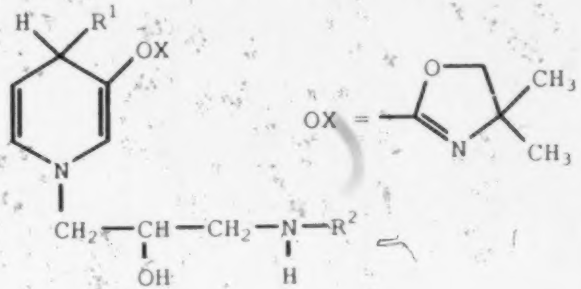
Table 1. Analytical data for 1-{1-[4-alkyl(aryl)-3-(4,4-dimethyloxazolin-2-yl)-1,4-dihydropyridyl]}-3-alkylamino-2-propanols.



Compd.	R^1	R^2	Yield, % Method A	Yield, % Method B	MP, °C	^aR_f	Formula	Exact mass Calcd.	Exact mass Found
146	Ph	$-C(CH_3)_3$	45	70	63-65	0.48	$C_{23}H_{33}N_3O_2$	383.2572	383.2574
147	Ph	$-CH(CH_3)_2$	33	68	73-75	0.46	$C_{22}H_{32}N_3O_2$	369.2416	369.2409
148	n-Bu	$-C(CH_3)_3$	35	63	oil	0.50	$C_{21}H_{37}N_3O_2$	363.2885	363.2871
149	n-Bu	$-CH(CH_3)_2$	30	60	oil	0.47	$C_{20}H_{35}N_3O_2$	349.2737	349.2725
150	Me	$-C(CH_3)_3$	38	65	oil	0.46	$C_{18}H_{31}N_3O_2$	321.2416	321.2409
151	Me	$-CH(CH_3)_2$	36	62	oil	0.45	$C_{17}H_{29}N_3O_2$	307.2259	3 07.2253

[a] Ether:methanol (7:3 v/v) as development solvent.

Table 2. Ir[a,b] and ^{1}H nmr[c,d] spectral data for 1-{1-[4-substituted-3-(4,4-dimethyloxazolin-2-yl)-1,4-dihydropyridyl]}-3-alkylamino-2-propanols.



Compd.	ir (cm^{-1}) (OH)	^{1}H nmr δ (ppm)
146[c]	3230[b]	1.08 and 1.24 (two s, 3H each, oxazolinyl methyls); 1.1 (s, 9H, -C($\underline{CH}_3$)$_3$; 2.15 (br s, 2H, OH, NH, exchange with deuterium oxide); 2.44 (d, J_{vic}= 8.1 Hz of d, J_{gem}= 12.5 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-); 2.78 (d, J_{vic}= 3.7 Hz of d, J_{gem} = 12.5 Hz, 1H, CH(OH)-C$\underline{H}$H^1-NH-); 3.30 [m, 2H, DHP-$\underline{CH}_2$-CH(OH)]; 3.72 (m, 1H, CH$_2$-$\underline{CH}$(OH)-CH$_2$); 3.79 and 3.86 (two d, $J_{gem.}$= 8.45 Hz, 1H each, oxazolinyl -O$\underline{CH}_2$); 4.69 (d, $J_{4,5}$= 5.0 Hz, 1H, DHP H-4); 4.86 and 4.90 (two d, $J_{5,6}$= 8.1 Hz of d, $J_{4,5}$=

Table 2. (cont.)

		5.0 Hz, (ratio 1:1), 1H total, DHP H-5); 6.04 and 6.08 (two d, d, $J_{5,6}$= 8.1 Hz of d, $J_{2,6}$= 1.60 Hz, (ratio 1:1), 1H total, DHP H-6), 6.84 and 7.04 (two d, $J_{2,6}$= 1.60 Hz, (1:1 ratio), 1H total, DHP H-2); 7.22-7.44 (m, 5H, phenyl hydrogens).
147^{c}	3238^{b}	1.05 (d, J= 7.5 Hz, 6H, -NH-CH(C$\underline{H}_3$)$_2$; 1.08 and 1.21 (two s, 3H each, oxazolinyl methyls); 2.2 (br s, 2H, OH, NH, exchange with deuterium oxide); 2.45 (d, J_{vic} = 8.8 Hz of d, J_{gem}= 12.1 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-); 2.75 (m, 2H, CH(OH)C$\underline{H}$H^1, C$\underline{H}$(CH$_3$)$_2$), 3.25 (m, 2H, DHP-C$\underline{H}_2$-); 3.7 [m, 1H, -$\underline{CH}$(OH)-]; 3.76 and 3.82 (two d, J_{gem}= 8.4 Hz, 1H each, OC$\underline{H}_2$); 4.64 (d, $J_{4,5}$= 5.1 Hz, 1H, DHP H-4); 4.82 and 4.85 (two d, $J_{5,6}$= 8.2 Hz of d, $J_{4,5}$= 5.0 Hz (ratio 1:1), 1H total, DHP H-5); 6.01 and 6.05 (two d, $J_{5,6}$= 8.2 Hz of d, $J_{2,6}$= 1.7 Hz (ratio 1:1), 1H total, DHP H-6), 6.97 and 7.00 (two d, $J_{2,6}$= 1.7 Hz (ratio 1:1), 1H total, DHP H-2); 7.22-7.44 (m, 5H, phenyl hydrogens).
148^{d}	3240^{a}	0.94 (distorted t, J= 7 Hz, 3H, -(CH$_2$)$_3$-C$\underline{H}_3$); 1.14 (s, 9H, NH-C(C$\underline{H}_3$)$_3$); 1.2-1.7 [m, 12H, -(C$\underline{H}_2$)$_3$-CH$_3$, oxazolinyl methyls]; 2.44 (d, J_{vic}= 8.7 Hz of d, J_{gem}= 11.7 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-); 2.6 (br s, 2H, OH, NH, exchange with deuterium oxide);

Table 2. (cont.)

		2.81 (d, J_{vic}= 3.5 Hz of d, J_{gem}= 11.7 Hz of d, $J_{CH,NH}$= 2.1Hz, 1H, -CH(OH)-$\mathrm{C\underline{H}H^1}$-NH-); 3.21 [d, J_{vic}= 6.3 Hz , 2H, DHP-$\mathrm{\underline{CH}_2}$-CH(OH)-]; 3.53 (m, 1H, DHP H-4); 3.70 [m, 1H, -$\mathrm{\underline{CH}}$(OH)-]; 3.86 and 3.94 (two d, J_{gem}= 8.4 Hz, 1H each, oxazolinyl, $\mathrm{OC\underline{H}_2}$); 4.70 (m, 1H, DHP H-5), 5.9 and 5.94 (two d, $J_{5,6}$= 8.2 Hz of d, $J_{2,6}$= 1.6 Hz (ratio 1:1), 1H total, DHP H-6); 6.84 and 6.86 (two d, $J_{2,6}$= 1.6 Hz, (ratio 1:1), 1H total, DHP H-2).
149^c	3254^a	0.87 (distorted t, J= 7 Hz, 3H, -$\mathrm{(CH_2)_3}$-$\mathrm{C\underline{H}_3}$); 1.07 [d, J= 7.0 Hz, 6H, NH-$\mathrm{CH(C\underline{H}_3)_2}$]; 1.27 (s, 6H, oxazolinyl methyls); 1.29-1.6 (m, 6H, -$\mathrm{(C\underline{H}_2)_3}$-$\mathrm{CH_3}$); 2.45 (d, J_{vic}= 8.0 Hz of d, Jgem= 11.7 Hz, 1H, -CH(OH)-$\mathrm{C\underline{H}H^1}$-NH-); 2.65 (br s, 2H, OH, NH, exchange with deuterium oxide); 2.79 (m, 2H, $\mathrm{C\underline{H}(CH_3)_2}$, -CH(OH)-$\mathrm{CH\underline{H}^1}$-NH-); 3.19 (d, J_{vic}= 6.3 Hz , 2H, DHP-$\mathrm{C\underline{H}_2}$-CH(OH)-); 3.51 (m, 1H, DHP H-4), 3.75 [m, 1H, $\mathrm{C\underline{H}}$(OH)-]; 3.86 and 3.93 (two d, J_{gem}= 7.2 Hz, 1H each, oxazolinyl -$\mathrm{OC\underline{H}_2}$); 4.65 and 4.6 (two d, $J_{5,6}$= 8.1 Hz of d, $J_{4,5}$= 5.0 Hz (ratio 1:1), 1H total, DHP H-5); 5.9 and 5.94 (two d, $J_{5,6}$= 8.1 Hz of d, $J_{2,6}$= 1.6 Hz, 1H total, DHP H-6); 6.82 and 6.84 (two d, $J_{2,6}$= 1.60 Hz (ratio 1:1), 1H total, DHP H-2).

Table 2. (cont.)

150^c	3287^a	1.1 [s, 9H, $C(C\underline{H}_3)_3$]; 1.14 (d, J= 6.0 Hz, 3H, DHP C-4 methyl); 1.27 and 1.30 [two s, 3H each, oxazolinyl methyls]; 2.44 (d, J_{vic}= 8.1 Hz of d, Jgem= 11.5 Hz, 1H, $C\underline{H}H^1$-NH-); 2.71 (m, 2H, NH, -CH(OH)-$CH\underline{H}^1$-NH-); 3.2 (d, J=6 Hz, 2H, DHP-$C\underline{H}_2$-); 3.4 (d, $J_{CH,OH}$= 6 Hz, 1H, OH); 3.75 [m, 1H, -$C\underline{H}$(OH)-]; 3.86 and 3.9 (two d, 1H each, oxazolinyl -$OC\underline{H}_2$); 4.72 and 4.76 (two d, $J_{5,6}$= 8.1 Hz of d, $J_{4,5}$= 5.0 Hz (ratio 1:1), 1H total, DHP H-5); 5.83 and 5.88 (two d, $J_{5,6}$= 8.1 Hz of d, $J_{2,6}$= 1.6 Hz, 1H total, DHP H-6); 6.83 and 6.86 (two d, $J_{2,6}$= 1.60 Hz (ratio 1:1), 1H total, DHP H-2).
151^d	3287^a	1.07 [d, J= 6.3 Hz, 6H, -$CH(C\underline{H}_3)_2$]; 1.14 (d, J= 6Hz, 3H, DHP C-4 methyl) ; 1.28 and 1.30 [two s, 3H each, oxazolinyl methyls]; 2.2 (br s, 2H, OH, NH); 2.46 (d, J_{vic}= 8.1 Hz of d, Jgem= 11.8 Hz, 1H, -CH(OH)-$C\underline{H}H^1$-NH-); 2.73 (d, J_{vic}= 3.1 Hz of d, Jgem= 11.8 Hz, 1H, CH(OH)-$CH\underline{H}^1$-NH-); 2.81 [m, 1H, NH-$C\underline{H}(CH_3)_2$]; 3.20 (d, J= 6.0 Hz, 2H, DHP-$C\underline{H}_2$-CH(OH)-]; 3.47 (m, 1H, DHP H-4); 3.79 [m, 1H, -$C\underline{H}$(OH)-]; 3.88 and 3.94 (two d, J_{gem}= 7.2 Hz, 1H each, oxazolinyl -$OC\underline{H}_2$); 4.67 and 4.73 (two d, $J_{5,6}$= 8.1 Hz of d, $J_{4,5}$= 5.0 Hz (ratio 1:1), 1H total, DHP H-5), 5.87 and 5.92 (two

d, $J_{5,6}$= 8.1 Hz of d, $J_{2,6}$= 1.6 Hz (ratio 1:1), 1H total, DHP H-6), 6.84 and 6.85 (two d, $J_{2,6}$= 1.60 Hz (ratio 1:1), 1H total, DHP H-2).

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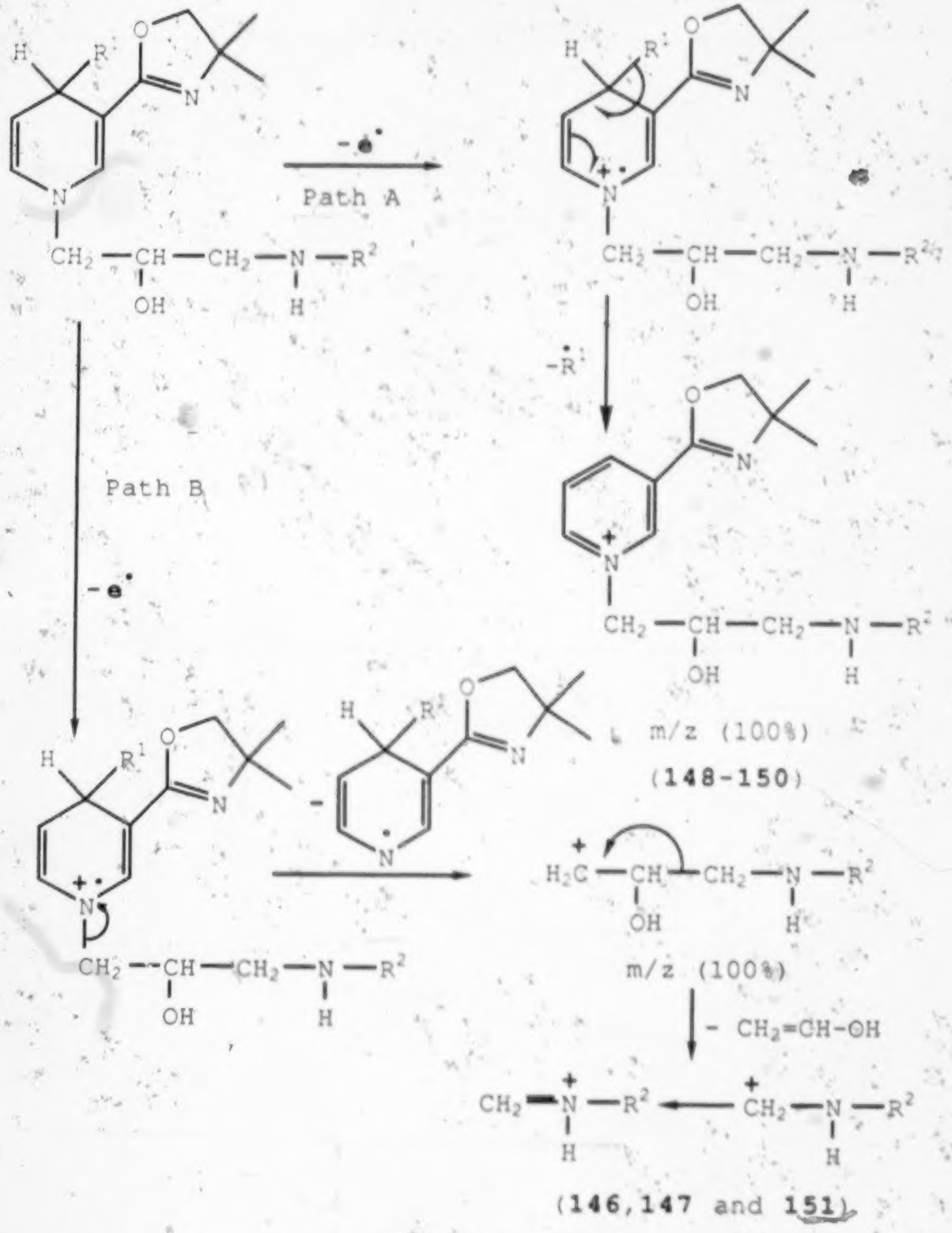
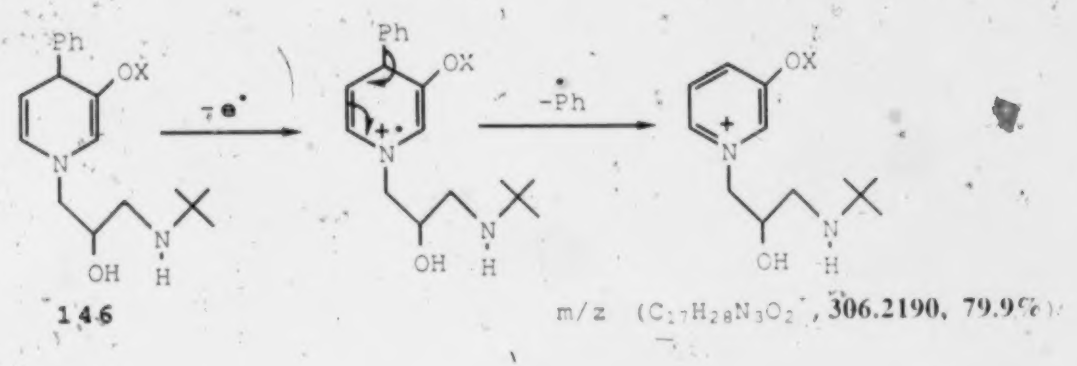
^{a}Film, ^{b}KBr, ^{c}CDCl$_3$, ^{d}CCl$_4$.


- e•
Path A
Path B
- e•
-R•1
m/z (100%)
(**148-150**)
m/z (100%)
- CH₂=CH-OH
(**146,147** and **151**)

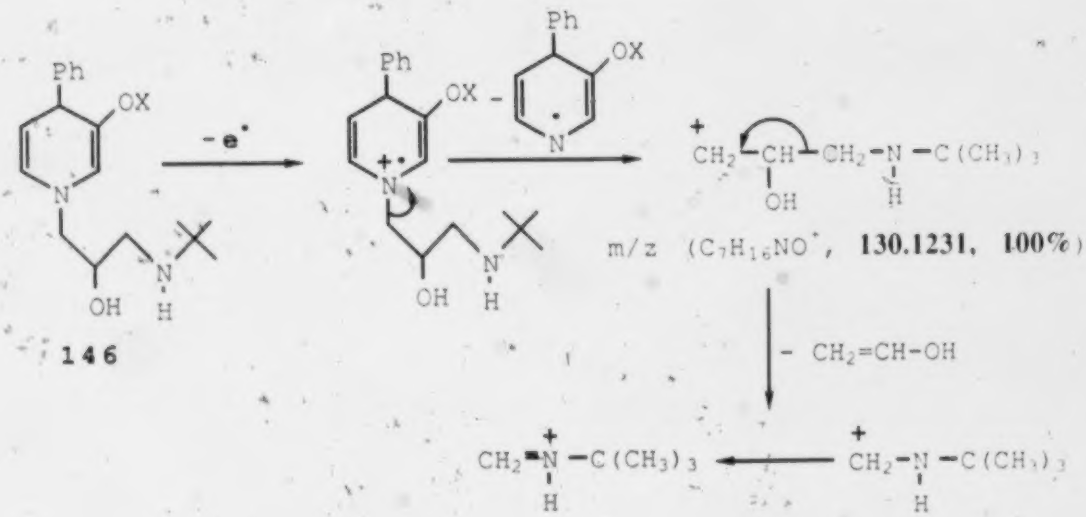
R^1= Ph, n-Bu, Me; R^2= $CH(CH_3)_2$, $C(CH_3)_3$

Scheme 5. The major fragmentation pathways for 1-{1-[4-alkyl (aryl)-3-(4,4-dimethyloxazolin-2-yl)]-1,4-dihydropyridyl}-3-alkylamino-2-propanols (**146-151**).

Path A.


Ph
OX
N
OH
H
146
- e•
-Ph
+•
+
m/z (C17H28N3O2+, 306.2190, 79.9%)

Path B.


Ph
OX
N
OH
H
146
- e•
+•
CH2-CH-CH2-N-C(CH3)3
m/z (C7H16NO+, 130.1231, 100%)
- CH2=CH-OH
CH2=N-C(CH3)3
CH2-N-C(CH3)3

Scheme 6. The major fragmentation pathways for 1-{1-[4-phenyl-3-(4,4-dimethyloxazolin-2-yl)]-1,4-dihydropyridyl}-3-t-butylamino-2-propanol (**146**).

3.1.2.0.0 SYNTHESIS OF 1-[1-(2-ALKYL-3-CYANO-1,2-DIHYDROPYRIDYL)]-3-ALKYLAMINO-2-PROPANOLS, and 1-[1-(6-ALKYL-3-CYANO-1,6-DIHYDROPYRIDYL)]-3-ALKYLAMINO-2-PROPANOLS.

Addition of 3-cyanopyridine (**152**) to an ethereal solution of an organolithium reagent (R^1-Li; R^1= t-Bu and n-Bu) at -78 °C afforded a mixture of 1,2- and 1,6-dihydropyridines (**153**)[444] which on hydrolysis with water yield the corresponding analogues (**154**). The ratios of 1,2-:1,6-dihydro products (**154**) are about 3:5 (t-BuLi) and 1:3 (n-Bu). Under these reaction conditions, no 1,4-dihydropyridyl product is produced. Since the 1,6-dihydropyridines are less soluble in ether:hexane (1:1 v/v), the mixture (**154**) can be separated to obtain the pure 1,2- and 1,6-isomers (**154a** and **154b**). The isomers (**154c** and **154d**) were similarly separated. The two synthetic methods (A and B) used to synthesize (**156-167**) are outlined in Scheme 7. The direct reaction of N-lithio-2-(and 6-)-alkyl-1,2-(and 1,6-)dihydropyridines (**153**) with epibromohydrin (method A) provided (**155**) in 40-50% yields, whereas reactions employing the pure 1,2- or 1,6-isomers (**154a** or **154b**) by method B gave 70-80% yields of (**155**). The physical data for (**156-167**) are presented in Table 3, and the ^{1}H nmr and ir spectroscopic data are summarized in Table 4. There are two chiral centers present in (**156-167**) which are likely a mixture of four diastereomers (RR, SS, RS, SR). The ^{1}H nmr spectra usually showed the presence of two different diastereomers (RR=SS and RS=SR) in a ratio of 1:1 (**156, 157, 159, 160, 167**).The ratios of the two diastereomers (^{1}H nmr) for compounds **161, 162** and **166** after purification of the diastereomeric mixture, were 2:1, 1:2 and 3:2, respectively. The diastereomeric mixture (**157**) was separated by tlc chromatography using ether:ethanol (7:3 v/v) as development solvent to give one pure diastereomer (**158**). The two diastereomeric mixtures **161** (2:1 ratio) and **162** (1:2 ratio) were successfully separated by multidevelopment tlc chromatography using ether:ethanol (7:3 v/v) as development solvent to afford two pure diastereomers (**163-164**) as shown in Table 3. The ^1H nmr spectrum (δ) of the pure diastereomer (**165**), as illustrated in Figure 10, indicated that the chiral carbon (CH$_X$OH) causes the adjacent methylene protons (H$_A$ and H$_B$; H$_{A'}$, and H$_{B'}$) to be chemically non-equivalent giving rise to ABX and A'B'X spin systems (4 lines). For example, H$_A$ (δ 2.36) and H$_B$ (δ 2.69) exhibit J_{gem} coupling constants of 12.2 Hz, whereas the vicinal coupling constants J_{AX} and J_{BX} were 8.4 and 3.75 Hz, respectively. The H$_{A'}$ (δ 3.26) and H$_{B'}$ (δ 3.25) protons showed J_{gem} coupling values of 15.0 Hz, and the vicinal coupling constants $J_{A'X}$ and $J_{B'X}$ were 6.5 and 3.75 Hz, respectively.

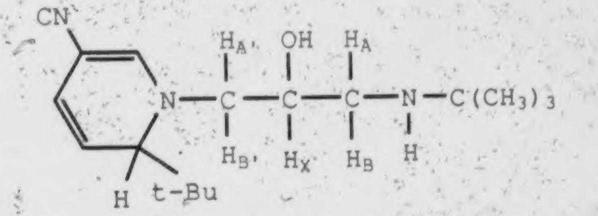


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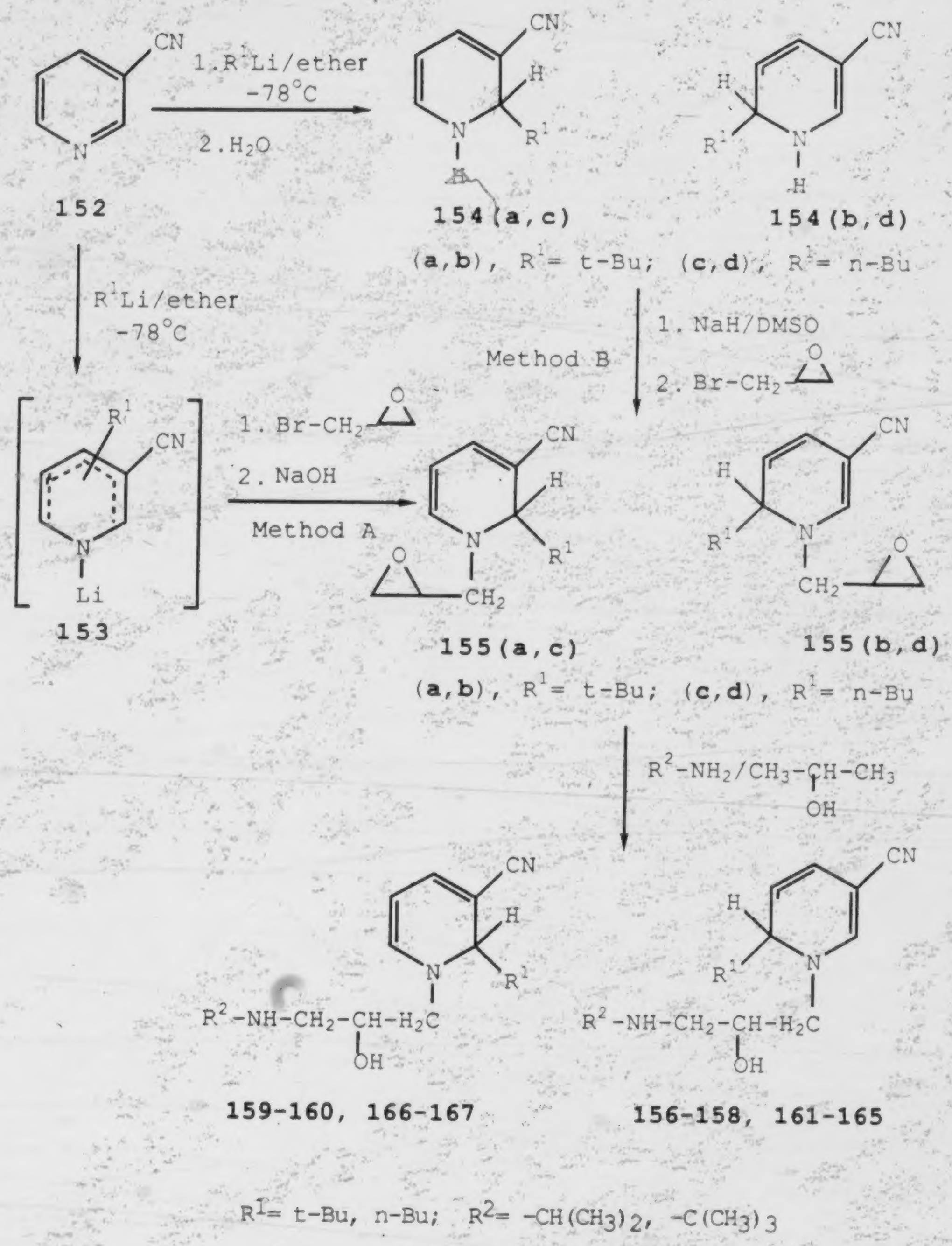
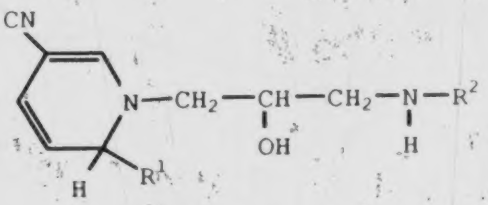
Figure 10. The coupling pattern for 1-{1-(6-t-butyl-3-cyano-1,6-dihydropyridyl)}-3-t-butylamino-2-propanol.

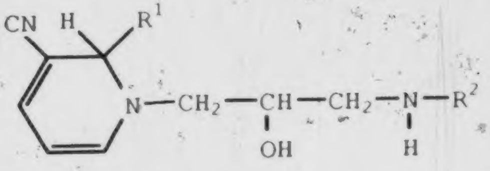

152
1. R^{1}Li/ether
-78°C
2. H$_2$O
154(a,c)
154(b,d)
(a,b), R^1= t-Bu; (c,d), R^1= n-Bu
R^{1}Li/ether
-78°C
153
1. NaH/DMSO
2. Br-CH$_2$
Method B
1. Br-CH$_2$
2. NaOH
Method A
155(a,c)
155(b,d)
(a,b), R^1= t-Bu; (c,d), R^1= n-Bu
R^2-NH$_2$/CH$_3$-CH-CH$_3$
OH
R^2-NH-CH$_2$-CH-H$_2$C
159-160, 166-167
156-158, 161-165
R^1= t-Bu, n-Bu; R^2= -CH(CH$_3$)$_2$, -C(CH$_3$)$_3$

Scheme 7. Synthesis of 1-{1-[2-(or 6-)alkyl-3-cyano)-1,2- or (1,6-) dihydropyridyl]}-3-alkylamino-2-propanols.

Table 3. Physical data for 1-{1-[2-(or 6-)-alkyl-3-cyano-1,2-(or 1,6-)-dihydropyridyl]}-3-alkylamino -2-propanols.



156-158, 161-165



159-160, 166-167

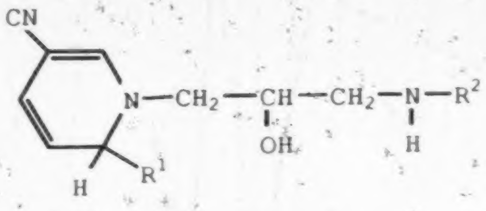
Compd.	R^1	R^2	Isomer	%yield Method A	Method B	Diastereomer Ratio	MP °C	R_f	Formula	Exact mass Calcd.	Found
156	n-Bu	$-CH(CH_3)_2$	1,6	40	70	1:1	oil	0.45^b	$C_{16}H_{27}N_3O$	277.2154	277.2155
157	n-Bu	$-C(CH_3)_3$	1,6	42	73	1:1	oil	0.46^b	$C_{17}H_{29}N_3O$	291.2310	291.2301
158	n-Bu	$-C(CH_3)_3$	1,6	-	25	SD^a	oil	0.50^b	$C_{17}H_{29}N_3O$	291.2310	291.2308
159	n-Bu	$-CH(CH_3)_2$	1,2	13	65	1:1	oil	0.50^b	$C_{16}H_{27}N_3O$	277.2154	277.2152
160	n-Bu	$-C(CH_3)_3$	1,2	16	70	1:1	oil	0.52^b	$C_{17}H_{29}N_3O$	291.2310	291.2306
161	t-Bu	$-CH(CH_3)_2$	1,6	-	33	2:1	oil	$0.50\text{-}0.55^b$	$C_{16}H_{27}N_3O$	277.2154	277.2152
162	t-Bu	$-CH(CH_3)_2$	1,6	-	30	1:2	oil	$0.40\text{-}0.50^b$	$C_{16}H_{27}N_3O$	277.2154	277.2152
163	t-Bu	$-CH(CH_3)_2$	1,6	-	22	SD	oil	$0.55\text{-}0.60^c$	$C_{16}H_{27}N_3O$	277.2154	277.2105

Table 3. (cont.)

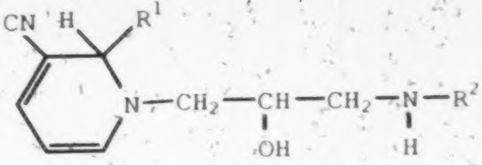
Compd.	R^1	R^2	Isomer	%yield Method A	Method B	Diastereomer Ratio	MP °C	R_f	Formula	Exact mass Calcd.	Found
164	t-Bu	$-CH(CH_3)_2$	1,6	-	27.5	SD	oil	0.46-0.50[c]	$C_{16}H_{27}N_3O$	277.2154	277.2145
165	t-Bu	$-C(CH_3)_3$	1,6	-	40	SD[a]	117	0.46-0.50[d]	$C_{17}H_{29}N_3O$	291.2310	291.2305
166	t-Bu	$-CH(CH_3)_2$	1,2	-	78	3:2	oil	0.5[d]	$C_{16}H_{27}N_3O$	277.2154	277.2155
167	t-Bu	$-C(CH_3)_3$	1,2	-	80	1:1	82-84	0.5[d]	$C_{17}H_{29}N_3O$	291.2310	291.2308

[a] SD= Only one single diastereomer could be isolated since the other diastereomer decomposed upon tlc purification. The tlc development solvent was: [b] Ether:methanol (7:3 v/v), [c] ether:methanol (8:2 v/v), and [d] ether:ethanol (7:3 v/v).

Table 4. Ir[a,b] and ^{1}H nmr[c] spectral data for 1-{1-[2-(or 6-)-alkyl-3-cyano-1,2-(or 1,6-)-dihydropyridyl]}-3-alkylamino-2-propanols.



157-158, 161-165



159-160, 166-167

Compd.	ir (cm^{-1}) (OH)	ir (cm^{-1}) (CN)	^{1}H nmr δ (ppm)
156	3418	2188[a]	0.92 [t, J= 7 Hz, 3H, -$(CH_2)_3$-C$\underline{H}_3$], 1.07 [two d, J= 6 Hz, 3H each, CH(C$\underline{H}_3)_2$]; 1.25-1.75 (m, 6H, -(C$\underline{H}_2)_3$-CH_3); 2.3-2.7 (br s, 2H, OH, NH exchange with deuterium oxide); 2.44 and 2.48 (two m (ratio 1:1), 1H total, CH(OH)-C$\underline{H}$H^1-NH-); 2.74 (m, 1H, CH(OH)-CHH$^{\underline{1}}$-NH-); 2.82 [m, 1H, -C$\underline{H}$$(CH_3)_2$]; 3.05 and 3.15 {two m, (ratio 1:1), 1H total, DHP-C$\underline{H}$H^1-CH(OH)}; 3.3 {m, 1H, DHP-CHH$^{\underline{1}}$-CH(OH)}; 3.80 (m, 1H, -CH_2-$\underline{CH}$(OH)-CH_2); 4.15 (m, 1H, DHP H-6); 5.03 and 5.04 (two m, 1H total, DHP H-5);

Table 4. (cont.)

		5.94 and 5.95 (two d, $J_{4,5}$= 9.4 Hz (ratio 1:1), 1H total, DHP H-4); 6.89 and 6.90 (two s, 1H total, DHP H-2).
157	3409, 2191[a]	0.90 [t, J= 7 Hz, 3H, -$(CH_2)_3$-C$\underline{H}_3$]; 1.10 [s, 9H, NH-C(C$\underline{H}_3$)$_3$]; 1.33 and 1.7 (two m, 6H, -(C$\underline{H}_2$)$_3$-CH_3); 2.0-3.0 (br s, 2H, OH, NH, exchange with deuterium oxide); 2.42 and 2.72 (two m, 1H each, CH(OH)-C$\underline{H}_2$-NH-); 3.02-3.38 [m, 2H, DHP-C$\underline{H}_2$-); 3.70 (m, 1H, -CH_2-C$\underline{H}$(OH)-CH_2); 4.14 (m, 1H, DHP H-6); 5.03 and 5.06 (two m, 1H total, DHP H-5); 5.94 (two d, $J_{4,5}$= 9.5 Hz, 1H, DHP H-4); 6.89 and 6.90 (two s (ratio 1:1); 1H total, DHP H-2).
158	3409, 2191[a]	0.92 [t, J= 7 Hz, 3H, -$(CH_2)_3$-C$\underline{H}_3$]; 1.12 [s, 9H, NH-C(C$\underline{H}_3$)$_3$]; 1.3 -1.7 (m, 6H, (C$\underline{H}_2$)$_3$-CH_3); 2.34 (br s, 2H, OH, NH, exchange with deuterium oxide); 2.45 (J_{vic}= 8.1 Hz of d, J_{gem}= 12.5 Hz, 1H, CH(OH)-C$\underline{H}H^1$-NH-); 2.76 (J_{vic}= 4.2 Hz of d, J_{gem}= 12.5 Hz, 1H, CH(OH)-CH$\underline{H}^1$-NH-); 3.06 [J_{vic}= 7.5 Hz of d, J_{gem}= 14.0 Hz, 1H, , DHP-C$\underline{H}H^1$-CH(OH)]; 3.36 [J_{vic}= 3.0 Hz of d, J_{gem}= 14.0 Hz, 1H, DHP-CH$\underline{H}^1$-CH(OH)]; 3.76 (m, 1H, -CH_2-C$\underline{H}$(OH)-CH_2); 4.16 (m, 1H, DHP H-6); 5.05

Tabl 4. (cont.)

		(d, $J_{4,5}$= 9.5 Hz, of d, $J_{5,6}$= 6.0 Hz, 1H, DHP H-5); 5.97 (d, $J_{4,5}$= 9.5 Hz, DHP H-4), 6.90 (s, 1H, DHP H-2).
159	3410, 2188^a	0.94 [t, 3H, J= 7 Hz, 3H, -$(CH_2)_3$-C$\underline{H}_3$]; 1.09 and 1.10 [two d, J= 7 Hz, 6H total, CH(C$\underline{H}_3)_2$]; 1.20-1.80 (m, 6H, -(C$\underline{H}_2)_3$-CH_3); 2.50 and 2.76 (two m, 1H each, CH(OH)-C$\underline{H}_2$-NH-); 2.65 (br s, 1H, NH, exchanges with deuterium oxide); 2.84 [m, 1H ,-C$\underline{H}$$(CH_3)_2$]; 3.08 (br s, 1H, OH, exchanges with deuterium oxide); 3.16 and 3.30 [two m, 1H each, DHP-C$\underline{H}_2$-CH(OH)]; 3.78 (m, 1H, -CH_2-C$\underline{H}$(OH)-CH_2); 4.16 and 4.18 (two t, J= 6.2 Hz, 1H total, DHP H-2); 4.9 and 4.92 (two d, $J_{4,5}$= 6.2 Hz of d, $J_{5,6}$= 6.2 Hz (ratio 1:1), 1H total, DHP H-5); 6.46 and 6.48 (two d (ratio 1:1), d, $J_{5,6}$= 6.2 Hz, 1H total, DHP H-6); 6.74 (d, $J_{4,5}$= 6.2 Hz 1H, DHP H-4).
160	3418, 2188^a	0.92 [t, J= 7 Hz, 3H, -$(CH_2)_3$-C$\underline{H}_3$]; 1.12 [s, 9H, NH-C(C$\underline{H}_3)_3$]; 1.25 -1.75 (m, 6H, -(C$\underline{H}_2)_3$-CH_3); 2.42 and 2.75 (two m, 1H each, CH(OH)-C$\underline{H}_2$-NH-); 3.15 and 3.30 [two m, 1H each, 2H, DHP-C$\underline{H}_2$-CH(OH)]; 3.66 (m, 1H, -CH_2-C$\underline{H}$(OH)-CH_2); 4.10 and 4.20 (two t (ratio 1:1), J= 6Hz, 1H, DHP H-2); 4.90 and 4.94 (two d, $J_{4,5}$= 6.5 Hz of d, $J_{5,6}$= 6.5 Hz (ratio 1:1), 1H total, DHP H-5), 6.48 (d, $J_{5,6}$= 6.5 Hz, 1H, DHP H-

Table 4. (cont.)

		6); 6.74 and 6.75 (two d, $J_{4,5}$= 6.5 Hz $J_{4,5}$= (ratio 1:1), 1H total, DHP H-4). Note: The OH and NH resonances were not visible in the spectrum propably due to the fact that they are very broad.
161	3418, 2196^{a}	0.89 (s, 9H, t-Bu); 1.06 and 1.08 (two d, J= 7 Hz (ratio 1:1), 6H total, -CH(C$\underline{H}_3$)$_2$]; 2.42 and 2.70 (two m, 1H each, CH(OH)-C$\underline{H}_2$-NH-); 2.76 [q, J= 7Hz, 1H, C$\underline{H}$(CH$_3$)$_2$]; 3.26 and 3.4 [two m (ratio 2:1), 2H total, DHP-C$\underline{H}_2$-CH(OH)]; 3.63 and 3.73 [two m (ratio 1:2), 1H total, -CH$_2$-C$\underline{H}$(OH)-CH$_2$]; 3.80 (d, $J_{5,6}$= 6 Hz, 1H, DHP H-6); 5.04 and 5.06 (two d, $J_{4,5}$= 9.5 Hz of d, $J_{5,6}$= 4.5 Hz (ratio 2:1), 1H total, DHP H-5); 6.12 (d, $J_{4,5}$= 9.5 Hz, 1H, DHP H-4); 7.00 and 7.04 (two s, (ratio 1:2), 1H total, DHP H-2).
162	3418, 2196^{a}	0.90 (s, 9H, t-Bu); 1.06 and 1.08 (two d (ratio 1:1), J= 7 Hz, 6H, -CH(C$\underline{H}_3$)$_2$]; 2.44 and 2.72 (two m, 1H each, CH(OH)-C$\underline{H}_2$-NH-); 2.80 [q, J= 7Hz, 1H, NH-C$\underline{H}$(CH$_3$)$_2$]; 3.26 and 3.46 [two m, 1H each, DHP-C$\underline{H}_2$-CH(OH)]; 3.67 and 3.74 (two m, (ratio 2:1), 1H total, -CH$_2$-C$\underline{H}$(OH)-CH$_2$); 3.82 (d, $J_{5,6}$= 5.0 Hz, 1H, DHP H-6); 5.04 and 5.06 (two d, $J_{4,5}$= 9.5 Hz of d, $J_{5,6}$= 5.0 Hz, 1H, DHP H-5); 6.12 (d, $J_{4,5}$= 9.5 Hz, 1H, DHP H-4); 7.02 and 7.04 (two s, (ratio 2:1), 1H total, DHP H-2).

Table 4. (cont.)

163	3418, 2196^a	0.88 (s, 9H, t-Bu); 1.06 and 1.08 (two d, J= 7 Hz, 6H, -CH(C$\underline{H}_3$)$_2$]; 2.18 (br s, 2H, N$\underline{H}$ and O$\underline{H}$, exchange with deuterium oxide); 2.47 (d, J_{gem}= 12.0 Hz of d, J_{vic} = 8.5 Hz, 1H, CH(OH)-C$\underline{H}$H^1-NH-); 2.74 (d, J_{gem}= 12.0 Hz of d, J_{vic}= 3.6 Hz, 1H, CH(OH)-CH$\underline{H}^1$-NH-); 2.82 [m, 1H, NH-C$\underline{H}$(CH$_3$)$_2$]; 3.32 [m, 2H, DHP-C$\underline{H}_2$-CH(OH)]; 3.76 [m, 1H, CH$_2$-C$\underline{H}$(OH)]; 3.82 (d, $J_{5,6}$= 6.0 Hz, 1H, DHP H-6); 5.05 (d, $J_{4,5}$= 9.5 Hz of d, $J_{5,6}$= 6.0 Hz, 1H, DHP H-5); 6.15 (d, $J_{4,5}$= 9.5 Hz, 1H, DHP H-4); 7.02 (s, 1H, DHP H-2).
164	3435, 2188^a	0.90 (s, 9H, t-Bu); 1.04 and 1.06 (two d, J= 6.1 Hz, 6H, -CH(C$\underline{H}_3$)$_2$]; 2.0-2.7 (br s, 2H, N$\underline{H}$ and O$\underline{H}$, exchange with deuterium oxide); 2.44 (d, J_{gem}= 12.3 Hz of d, J_{vic} = 8.5 Hz, 1H, CH(OH)-C$\underline{H}$H^1-NH-); 2.72 (d, J_{gem}= 12.3 Hz of d, J_{vic}= 3.8 Hz, 1H, CH(OH)-CH$\underline{H}^1$-NH-); 2.78 [q, J= 6.1 Hz, 1H, -CH$_2$-NH-C$\underline{H}$(CH$_3$)$_2$]; 3.28 [m, 2H, DHP-C$\underline{H}_2$-CH(OH)]; 3.74 (m, 1H, CH$_2$-C$\underline{H}$(OH)-CH$_2$-); 3.81 (d, $J_{5,6}$= 6.1 Hz, 1H, DHP H-6); 5.04 (d, $J_{4,5}$= 9.15 Hz of d, $J_{5,6}$= 6.1 Hz, 1H, DHP H-5); 6.12 (d, $J_{4,5}$= 9.15 Hz, 1H, DHP H-4); 7.02 (s, 1H, DHP, H-2).

Table 4. (cont.)

165	3418, 2188^b	0.90 [s, 9H, DHP-t-Bu]; 1.08 (s, 9H, -NH-C(C$\underline{H}_3$)$_3$); 2.2 (br s, 2H, N$\underline{H}$ and O$\underline{H}$, exchange with deuterium oxide); 2.36 (d, J_{gem}= 12.2 Hz of d, J_{vic}= 8.4 Hz, 1H, CH(OH)-C$\underline{H}$H^1-NH-); 2.69 (d, J_{gem}= 12.2 Hz of d, J_{vic}= 3.75 Hz, 1H, CH$\underline{H}^1$-NH-); 3.26 [d, J_{gem}= 15.0 Hz of d, J_{vic}= 6.5 Hz , 1H, and d, J_{vic}= 3.75 Hz of d, J_{gem}= 15.0 Hz, 1H; DHP-C$\underline{H}$H^1-CH(OH)]; 3.35 (d, J_{gem}= 15.0 Hz of d, J_{vic}= 3.75 Hz, 1H; DHP-CH$\underline{H}^1$-CH(OH); 3.65 (m, 1H, -CH$_2$-$\underline{CH}$(OH)-CH$_2$); 3.82 (d, $J_{5,6}$= 6.0 Hz, 1H, DHP H-6); 5.03 (d, $J_{4,5}$= 9.5 Hz of d, $J_{5,6}$= 6.0 Hz, 1H, DHP H-5); 6.12 (d, $J_{4,5}$= 9.5 Hz, 1H, DHP H-4); 7.02 (s, 1H, DHP H-2).
166	3427, 2188^a	0.95 (s, 9H, DHP t-Bu); 1.06 and 1.08 (two d, J= 7 Hz, 6H total, -CH(C$\underline{H}_3$)$_2$]; 2.65 and 2.74 (two m, 2H total, CH(OH)-C$\underline{H}_2$-NH-); 2.65 (br s, 2H, N$\underline{H}$ and O$\underline{H}$, exchange with deuterium oxide); 2.81 [m, 1H, NH-C$\underline{H}$(CH$_3$)$_2$]; 3.24 and 3.46 [two m, 2H total, DHP-C$\underline{H}_2$-CH(OH)]; 3.68 and 3.76 [two m (ratio 3:2), 1H total, -CH$_2$-C$\underline{H}$(OH)-CH$_2$]; 3.92 and 3.94 (two s, (ratio 2:3), 1H total, DHP H-2); 4.97 and 5.0 (two d, $J_{4,5}$= 6.25 Hz of d, $J_{5,6}$= 6.25 Hz (ratio 3:2), 1H total, DHP H-5); 6.58 and 6.62 (two d, $J_{5,6}$= 6.25 Hz (ratio 3:2), 1H total, DHP H-6); 6.90 (d, $J_{4,5}$= 6.25 Hz, 1H, DHP H-4).

Table 4. (cont.)

167	3330, 2183^b	0.95 (s, 9H, DHP t-Bu); 1.08 [s, 9H, -NH-C(C$\underline{H}_3$)$_3$]; 2.35 (d, J_{gem}= 12.1 Hz of d, J_{vic}= 8.5 Hz, 1H, CH(OH)-C$\underline{H}$H^1-NH-); 2.0-3.0 (br s, 2H, N$\underline{H}$ and O$\underline{H}$, exchange with deuterium oxide); 2.7 (m, 1H, CH$\underline{H}^1$-NH-); 3.22 and 3.48 [two m, 1H each, DHP-C$\underline{H}_2$-CH(OH)]; 3.58 and 3.68 [two m (ratio 1:1), 1H total, -CH$_2$-C$\underline{H}$(OH)-CH$_2$]; 3.87 and 3.95 (two s (ratio 1:1), 1H total, DHP-2); 4.93 and 4.95 (two d, $J_{5,6}$= 6.0 Hz of d, $J_{4,5}$= 6.0 Hz, 1H total, DHP H-5); 6.59 and 6.0 (two d, $J_{5,6}$= 6.0 Hz (ratio 1:1), 1H total, DHP H-6); 6.89 and 6.90 (two d, $J_{4,5}$= 6.0 Hz (ratio 1:1), 1H total, DHP H-4).

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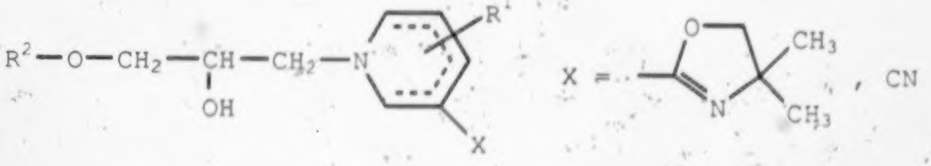
^{a}Film

^{b}KBr

^{c}CDCl$_3$

3.2.0.0.0 SYNTHESIS OF 1-ARYLOXY-3-(1-[2-, (4- OR 6-)-ALKYL-(ARYL)-3-SUBSTITUTED)]-1,2-(1,4- or 1,6-)-DIHYDROPYRIDYL)-2-PROPANOLS.

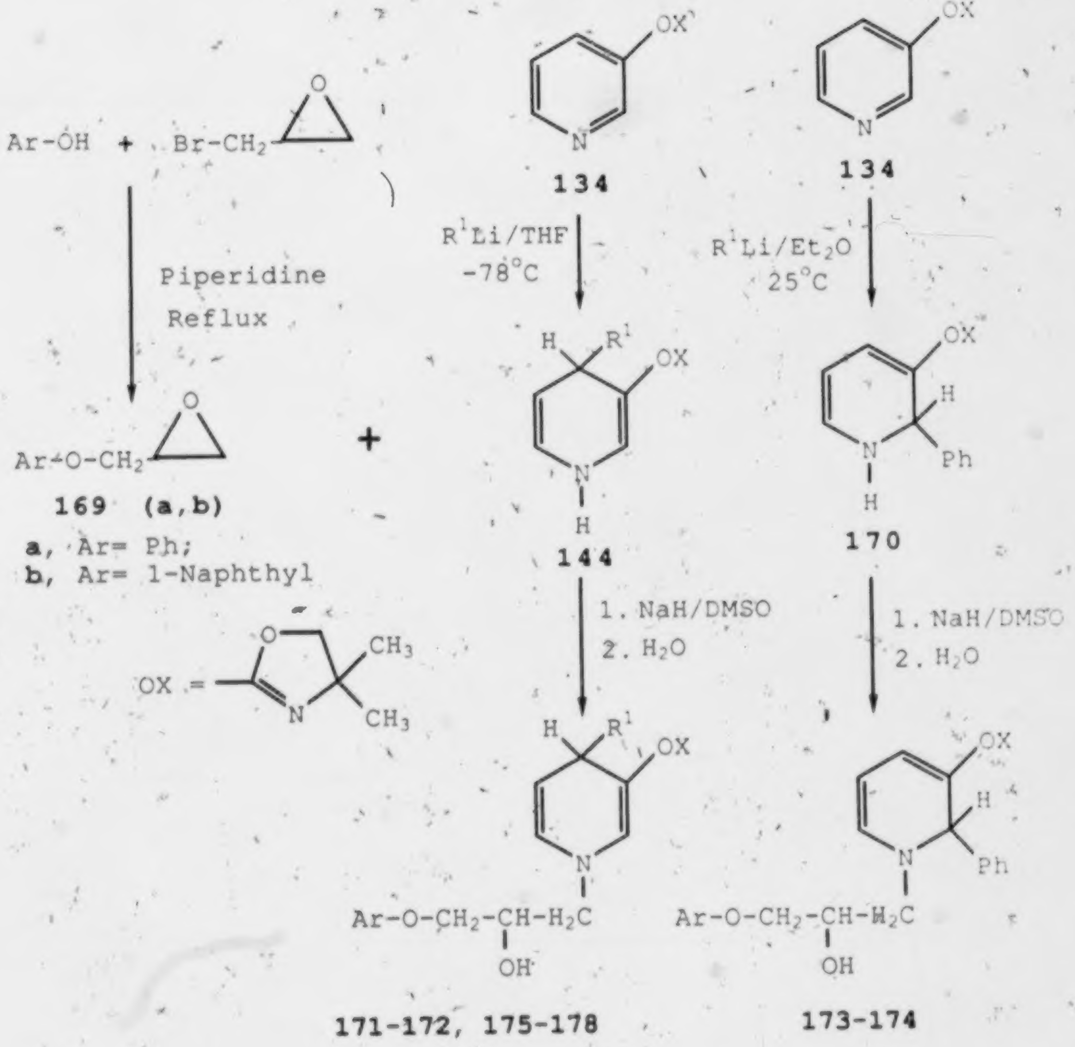
Replacement of the secondary alkylamino moieties of aryloxypropanolamines by tertiary amino groups has provided a large number of active compounds with a broad spectrum of biological activities[330] It was therefore of interest to prepare a series of compounds in which the alkylamino group of aryloxypropanolamines was replaced by a 1,2-, 1,4-, or 1,6-dihydropyridine moiety (**168**) to investigate the effect of terminal 1,2-, 1,4- and 1,6-dihydropyridine ring systems upon β-adrenergic antagonist activity.



168

3.2.1.0.0 SYNTHESIS OF 1-ARYLOXY-3-(1-[2-(OR 4-)ALKYL(ARYL)-3-(4,4-DIMETHYLOXAZOLIN-2-YL)-1,2-(or 1,4)-DIHYDROPYRIDYL])-2-PROPANOLS.

This class of compounds was prepared by the reaction of a 1-aryloxy-2,3-epoxypropane (**169**), that was prepared using a literature procedure[445,446] in 40% (Ar= Ph) and 20% (Ar= 1-naphthyl) yield, with a pure N-unsubstituted 1,4-dihydropyridine (**144**) or a pure N-unsubstituted-1,2-dihydropyridine (**170**)[431] in DMSO solution in the presence of NaH to afford the target compounds (**171-178**) as illustrated in Scheme 8.

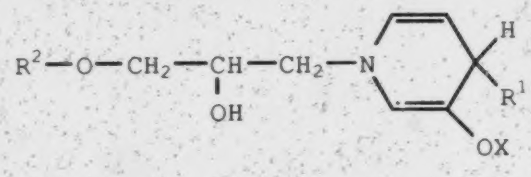

Ar-OH + Br-CH$_2$
Piperidine
Reflux
Ar-O-CH$_2$
169 (a,b)
a, Ar= Ph;
b, Ar= 1-Naphthyl
OX =
CH$_3$
CH$_3$
134
R^{1}Li/THF
-78°C
144
1. NaH/DMSO
2. H$_2$O
171-172, 175-178
134
R^{1}Li/Et$_2$O
25°C
170
1. NaH/DMSO
2. H$_2$O
173-174
Ar-O-CH$_2$-CH-H$_2$C
OH
OX
R^1
Ph

Ar= Ph, 1-Naphthyl; R^1= Ph, n-Bu, Me; Ar= Ph, 1-Naphthyl; R^1= Ph.

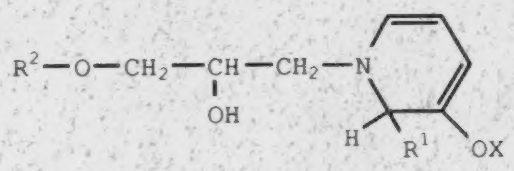
Scheme 8. Synthetic routes used for the synthesis of 1-aryloxy-3-{1-[2-(or 4-)alkyl(aryl)-3-(4,4-dimethyloxazolin-2-yl)]-1,2-(or 1,4-)dihydropyridyl]}-2-propanols.

Compound (**170**) was prepared by the reaction of (**134**) with phenyllithium in ether at 25 ^{o}C which afforded a mixture of the 1,4- and the predominate 1,2-dihydropyridine product. These two isomers were separated by recrystallization from ether: hexane (1:1 v/v) which gave pure 1,4-dihydropyridine (**144a**) in 18% yield. Further recrystallization from ether:hexane (3:7 v/v) gave pure (**170**) in (65%) yield. The reaction of N-unsubstituted-1,4-dihydropyridines (**144**) and N-unsubstituted-1,2-dihydropyridines (**170**) with 1-aryloxy-2,3-epoxypropanes (**169**) provided higher yields of (**171-178**) than the related reactions of the N-lithio-dihydropyridines (**143**) with (**169**). All of the products (**171-173**) and (**175-178**) prepared in this way (Scheme 8) were obtained as a mixture of two different diastereomers [RR(SS) and RS(SR) in a ratio of 1:1] as indicated by the ^{1}H nmr spectroscopy (see data in Table 6). In contrast, 1-(1-naphthyloxy)-3-(1-[2-phenyl-3-(4,4-dimethyloxazolin-2-yl)-1,2-dihydropyridyl])-2-propanol (**174**) was isolated as a single diastereomer {RR(SS) or RS(SR)} by column chromatography using ether:hexane (8:2 v/v) as eluant, or by preparative silica gel tlc chromatography using ether:hexane (7:3 v/v) as development solvent. The physical data for (**171-178**) are summarized in Table 5, and the ir and ^{1}H nmr are presented in Table 6. Interpretation of the mass spectra for (**171-178**) indicated that expulsion of the C-2 or C-4 alkyl(or aryl) substituent present on the dihydropyridyl ring system was a major fragmentation as shown in Scheme 6 Path A. Less important fragmentations included the loss of the N-alkyl substituent and cleavage of the N-substituted side chain as illustrated previously in Scheme 6 Path B.

Table 5. Physical data for 1-aryloxy-3-{1-[2-phenyl-3-(4,4-dimethyloxazolin-2-yl)]-1,2 -dihydropyridyl}-2-propanols and 1-aryloxy-3-{1-[4-substituted-3-(4,4-dimethyloxazolin-2-yl)]-1,4 -dihydropyridyl}-2-propanols.



171-172, 175-178



173-174

Compd.	R2	R1	aIsomer	% Yield Method A	MP, °C	R_f	Formula	Exact mass Calcd.	Exact mass Found	Microanalyses: Found (Calcd.) %C	%H	%N
171	Ph	Ph	1,4	83	55	0.50^b	$C_{25}H_{28}N_2O_3$	404.2090	404.2090			
172	1-Naphthyl	Ph	1,4	85	77	0.60^c	$C_{29}H_{30}N_2O_3$	454.2256	454.2259			
173	Ph	Ph	1,2	82	45	0.55^b	$C_{25}H_{28}N_2O_3$	404.2090	404.2101			
174	1-Naphthyl	Ph	1,2	42	oil	0.63^b	$C_{29}H_{30}N_2O_3$	454.2256	454.2256	76.39	6.94	5.89
										(76.56)	(6.65)	(5.89)
175	Ph	n-Bu	1,4	79	oil	0.52^b	$C_{23}H_{32}N_2O_3$	384.2412	384.2396			

Table 5. (cont.)

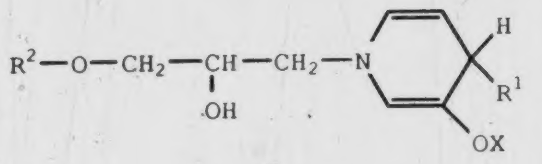
^{a}Compd.	R^2	R^1	^{b}Isomer	% Yield Method A	MP, ^{o}C	R_f	Formula	Exact mass Calcd.	Exact mass Found	Microanalyses: Found (Calcd.) %C	%H	%N
176	1-Naphthyl	n-Bu	1,4	80	52-53	0.62^c	$C_{27}H_{34}N_2O_3$	434.2569	434.2553	74.54	7.87	6.04
										(74.62)	(7.89)	(6.45)
177	Ph	Me	1,4	81	oil	0.48^c	$C_{20}H_{26}N_2O_3$	342.1943	342.1941	69.85	7.72	7.97
										(70.14)	(7.66)	(8.18)
178	1-Naphthyl	Me	1,4	83	oil	0.58^d	$C_{24}H_{28}N_2O_3$	392.2099	392.2092	73.43	7.19	7.14
										(73.44)	(7.19)	(7.14)

---

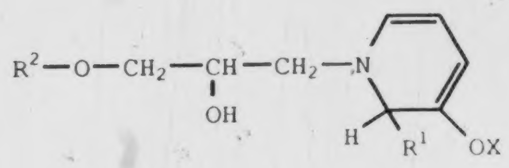
[a] All of the products (**171-173, 175-178**) existed as a mixture of two different diastereomers [RR(SS) and RS(SR)], as indicated by ^{1}H nmr spectrometry, in a ratio 1:1 except for compound (**174**) which existed as a single diastereomer.

[a] Ether:hexane (7:3 v/v), [b] ether:hexane (8:2 v/v) as tlc development solvent.

Table 6. Ir^{a,b} and ^{1}H nmr^c spectral data for 1-aryloxy-3-{1-[2 -(or 4-)alkyl(or phenyl)-3-(4,4-dimethyloxazolin-2-yl)-1,2-(or 1,4-) dihydropyridyl]}-2 - propanols.



171-172, 175-178



173-174

Compd.	ir (cm^{-1}) (OH)	^{1}H nmr δ (ppm)
171	3402^b	1.06 and 1.2 (two s, 3H each, oxazolinyl methyls); 3.0 (br s, 1H, OH); 3.45 (complex m, 2H, -CH(OH)-C$\underline{H}_2$-DHP); 3.76 (m, 2H, oxazolinyl -OC$\underline{H}_2$-); 3.95 (m, 2H, -O-C$\underline{H}_2$-CH(OH)-); 4.12 [m, 1H, -O-CH$_2$-C$\underline{H}$(OH)-]; 4.64 (d, $J_{4,5}$= 5.3 Hz, 1H, DHP H-4); 4.82 and 4.84 [two d, $J_{5,6}$= 6.9 Hz of d, $J_{4,5}$= 5.3 Hz, 1H total, DHP H-5]; 5.96 and 6.02 [two d (ratio 1:1), $J_{5,6}$= 6.9 Hz, 1H total, DHP H-6]; 6.90 and 6.92 [two s (ratio 1:1), 1H total, DHP H-2]; 6.96-7.4 (m, 10H, phenyl hydrogens).

Table 6. (cont.)

172	3400[b]	1.02 and 1.16 (two s, 3H each, oxazolinyl methyls); 3.47 (complex m, 2H, $-CH(OH)-\underline{C}\underline{H}_2-DHP$); 3.63 and 3.67 (two m, 2H total, oxazolinyl $-OC\underline{H}_2-$); 4.01 [m, 2H, $-O-C\underline{H}_2-CH(OH)-$]; 4.17 [m, 1H, $CH_2-C\underline{H}(OH)-$]; 4.66 (d, $J_{4,5}$= 5.4 Hz, 1H, DHP H-4), 4.78 and 4.80 (two d, $J_{5,6}$= 7.8 Hz of d, $J_{4,5}$= 5.4 Hz, 1H total, , 1H, DHP H-5), 5.96 and 5.98 (two d (ratio 1:1), $J_{5,6}$= 7.8 Hz, 1H total, DHP H-6), 6.68 and 6.72 (two s, (ratio 1:1), 1H total, DHP H-2); 7.1-8.3 (m, 12 H, napthyl and phenyl hydrogens).
173	3412[b]	1.2 and 1.3 (two s, 3H each, oxazolinyl methyls); 3.2 (br s, 1H, [illegible], exchanges with deuterium oxide), 3.3 and 3.46 (two m, 2H total, $CH(OH)-C\underline{H}_2-DHP$) ; 3.88 (m, 2H, oxazolinyl $-OC\underline{H}_2-$); 3.92 [m, 2H, $-O-C\underline{H}_2-CH(OH)-$]; 4.1 and 4.26 [two m (ratio 1:1), 1H total, $-O-CH_2-C\underline{H}(OH)-$]; 4.88 and 4.92 [two d (ratio 1:1), $J_{5,6}$= 6.6 Hz of d, $J_{4,5}$= 6.6 Hz, 1H total, DHP H-5), 5.76 and 5.78 [two s (ratio 1:1), 1H total, DHP H-2]; 6.52 and 6.56 (two d, $J_{5,6}$= 6.60 Hz (ratio 1:1); 1H total, DHP H-6), 6.80 and 6.82 (two d, $J_{4,5}$= 6.6 Hz (ratio 1:1), 1H, DHP H-4); 6.86-7.6 (m, 10H, phenyl hydrogens).
174	3418[a]	1.2 and 1.28 (two s, 3H each, oxazolinyl methyls); 2.7 (br s, 1H, OH); 3.5 and 3.65 (two complex m, $CH(OH)-C\underline{H}_2-DHP$) ; 3.90 (s, 2H, oxazolinyl $-OC\underline{H}_2-$); 4.14 [m, 2H, -O-

Table 6. (cont.)

		$C\underline{H}_2$-CH(OH)-]; 4.44 [m , 1H , -O-CH_2-$C\underline{H}$(OH)-]; 4.92 (d, $J_{5,6}$= 6.7 Hz of d, $J_{4,5}$= 6.7 Hz, 1H, DHP H-5); 5.86 (s, 1H, DHP H-2); 6.59 (d, $J_{5,6}$= 6.7 Hz, 1H , DHP H-6); 6.85 (d, $J_{4,5}$= 6.7 Hz, 1H, DHP H-4); 6.8 and 7.3-8.22 (m, 12 H, napthyl and phenyl hydrogens).
175	3400[a]	0.85 [t, J= 7Hz, 3H, -$(CH_2)_3$-$C\underline{H}_3$]; 1.15-1.7 (m, 12H, oxazolinyl methyls, -$(C\underline{H}_2)_3$-CH_3); 3.37 (complex m, 3H, -CH(OH)-$C\underline{H}_2$-DHP, OH); 3.49 (m, 1H, DHP H-4); 3.85 (m, 2H, oxazolinyl -O$C\underline{H}_2$-); 3.99 [m, 2H, -O-$C\underline{H}_2$-CH(OH)-]; 4.11 [m, 1H, -O-CH_2-$C\underline{H}$(OH)-]; 4.64 and 4.66 (two d, $J_{5,6}$= 8.2 Hz of d, $J_{4,5}$= 5.4 Hz (ratio 1:1), 1H total, DHP H-5); 5.93 (two d, $J_{5,6}$= 8.2 Hz (ratio 1:1), 1H total, DHP H-6); 6.86 and 6.88 [two s (ratio 1:1), 1H total, DHP H-2]; 6.9-7.34 (m, 10H, phenyl hydrogens).
176	3416[b]	0.84 [t, J= 7 Hz, 3H, -$(CH_2)_3$-$C\underline{H}_3$]; 1.15-1.65 (m, 12H, oxazolinyl methyls, $(C\underline{H}_2)_3$-CH_3); 3.2 (br s, 1H, OH); 3.4 (m, 2H, -CH(OH)-$C\underline{H}_2$-DHP); 3.48 (m, 1H, DHP H-4); 3.75 (m, 2H, oxazolinyl -O$C\underline{H}_2$-); 4.1 (m, 2H, -O-$C\underline{H}_2$-CH(OH)-); 4.2 [m, 1H, O-$CH_2C\underline{H}$(OH)-]; 4.62 and 4.65 (two d, $J_{5,6}$= 8.2 Hz of d, $J_{4,5}$= 4.5 Hz (ratio 1:1), 1H total, DHP H-5); 5.88 and 5.92 (two d, $J_{5,6}$= 8.2 Hz (ratio 1:1), 1H total, DHP H-6);

Table 6. (cont.)

		6.76 (d, J= 7.6 Hz, 1H, napthyl H-2); 6.92 and 6.96 (two s, (ratio 1:1), 1H total, DHP H-2); 7.35 (t, J= 7.6 Hz, 1H , naphtyl H-3); 7.4-7.56 (m, 3H, napthyl H-4, H-6, H- 7); 7.82 (m, 1H, napthyl H-5); 8.3 (m, 1H, napthyl H-8).
177	3328[a]	1.14 (d, J=7 Hz, 3H, DHP C-4 methyl); 1.25 and 1.27 (two s, 3H each, oxazolinyl methyls); 3.24 (br s, 1H, OH, exchanges with deuterium oxide); 3.37 (m, 2H, -CH(OH)-C$\underline{H}_2$-DHP); 3.46 (m, 1H, DHP H-4), 3.84 (m, 2H, oxazolinyl -OCH$_2$-); 3.98 (m, 2H, -O-C$\underline{H}_2$-CH(OH)-); 4.11 [m, 1H, -O-CH$_2$-C$\underline{H}$(OH)-]; 4.7 and 4.73 (two d, $J_{5,6}$= 8.1 Hz of d, $J_{4,5}$= 5.1 Hz (ratio 1:1), 1H total, DHP H-5); 5.83 and 5.86 (two d, $J_{5,6}$= 8.1 Hz (ratio 1:1), 1H total, DHP H-6); 6.81 and 6.82 (two s, (ratio 1:1), 1H total, DHP H-2); 6.9-7.4 (m, 5 H, phenyl hydrogens).
178	3332[a]	1.14 (d, J= 6.6 Hz, 3H, DHP C-4 methyl); 1.24 and 1.26 (two s, 3H each, oxazolinyl methyls); 3.2 (br s, 1H, OH); 3.46 (m, 2H, -CH(OH)-C$\underline{H}_2$-DHP); 3.54 (m, 1H, DHP H-4), 3.80 (m, 2H, oxazolinyl O$\underline{CH}_2$-); 4.14 (m, 2H, -O-C$\underline{H}_2$-CH(OH)-); 4.25 [m, 1H, O-CH$_2$-$\underline{CH}$(OH)-]; 4.7 (d, $J_{5,6}$= 8.0 Hz of d, $J_{4,5}$= 5.0 Hz, 1H, DHP H-5); 5.87 and 5.88 (d, $J_{5,6}$= 8.0 Hz of d, $J_{2,6}$= 1.6 Hz (ratio 1:1), 1H total, DHP H-6); 6.82 (d, J= 7.9

Table 6. (cont.)

Hz, 1H, napthyl H-2); 6.86 and 6.88 (two d, $J_{2,6}$= 1.6 Hz (ratio 1:1), 1H total, DHP H-2); 7.4 (t, J= 7.9 Hz, 1H, naphtyl H-3); 7.46-7.60 (m, 3H, napthyl H-4, H-6, H- 7); 7.85 (m, 1H, naphtyl H-5); 8.26 (m, 1H, naphtyl H-8).

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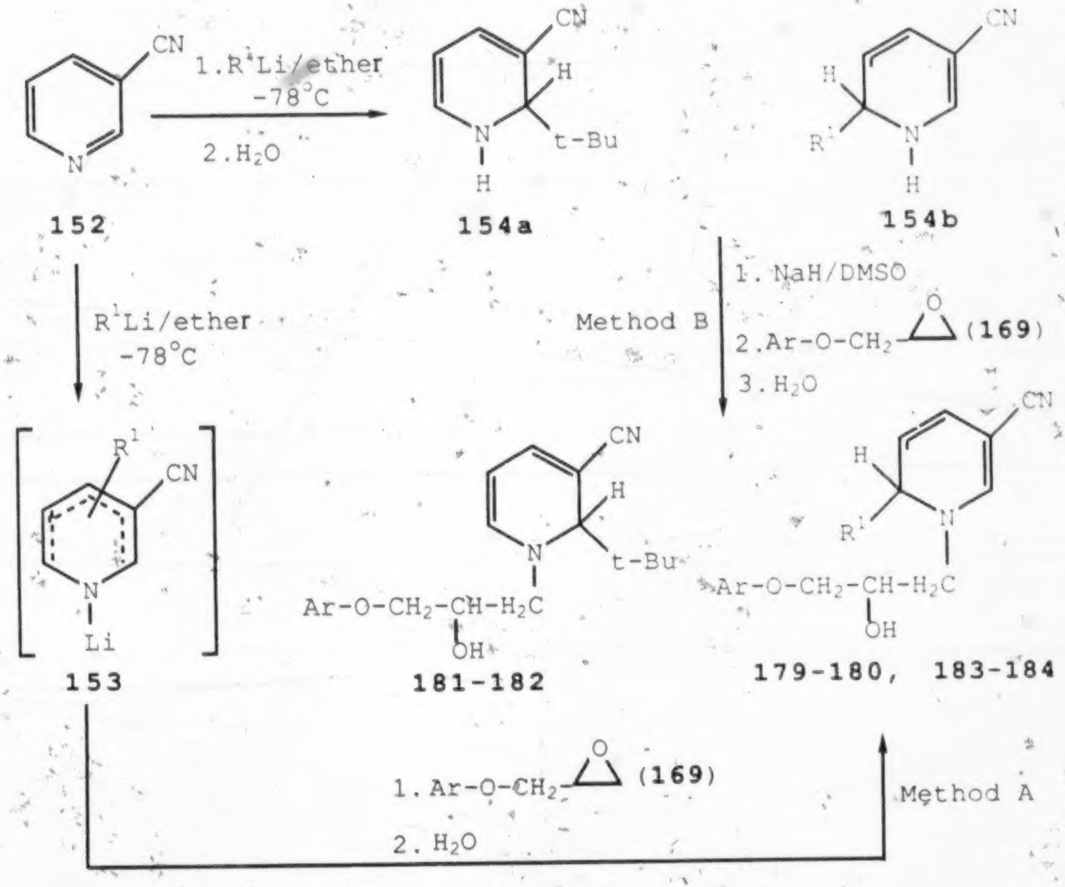
[a]Film, [b]KBr, [c]$CDCl_3$

3.2.2.0.0 SYNTHESIS OF 1-ARYLOXY-3-{1-[2-(or 6-)ALKYL-3-CYANO -1,2-(or 1,6-)DIHYDROPYRIDYL]}-2-PROPANOLS.

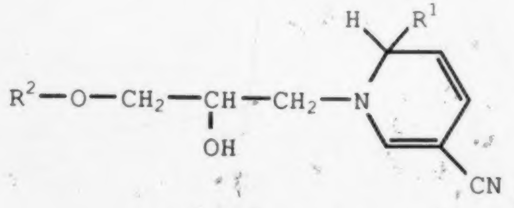
The reaction of N-unsubstituted 1,2- or 1,6-dihydropyridines (**154**, R^1= n-Bu, t-Bu)[431] with a 1-aryloxy-2,3-epoxypropane (**169**)[445,446] in DMSO solution in the presence of NaH afforded (**179-184**) in 70 to 80% yields (method B). Similar reactions employing (**153**) (method A) gave lower yields of the respective products as illustrated in Scheme 9. The physical data for (**179-184**) are summarized in Table 7. ^{1}H nmr and ir spectral data are presented in Table 8. The ir spectra for (**179-184**) showed a free OH absorption band in the 3410-3427 cm^{-1} range, and a strong absorption in the 2188-2196 cm^{-1} range for the CN group. The mass spectra for (**179-184**) showed the major important fragmentation is the loss of the C-2 or C-6 alkyl group which provided the base peak as illustrated previously in Scheme 6 Path A. In the case of compound (**182**), the largest mass ion $[M-57]^+$ present was attributed to the loss of a C-2 t-butyl radical, whereas the base peak originated from the loss of the N-substituted side chain. This fragmentation has been attributed to the steric strain of the t-Bu group present on the 1,2-dihydropyridine[447]. Examination of the ^{1}H nmr (δ) spectra for compounds (**179-184**) indicated that the oxygen methylene protons (O-$\underline{CH_2}$-) exhibited the same chemical shift, whereas the methylene protons attached to the dihydropyridyl nitrogen were chemically and magnetically non-equivalent. The ^{1}H nmr spectra for compounds (**179-184**) indicated the presence of two different diastereomers [RR(SS) and SR(RS)] in a ratio 1:1, except for (**180**) and (**183**) where the ratio was 1:2. These diastereomeric mixtures were obtained after preparative tlc purification on silica gel G plates with ether:hexane (7:3, v/v) as the development solvent using the multiple development tlc technique. Attempts to separate the two diastereomers were unsuccessful.


152
1.R^1Li/ether
-78°C
2.H_2O
154a
154b
R^1Li/ether
-78°C
153
Method B
1. NaH/DMSO
2.Ar-O-CH_2- (169)
3.H_2O
181-182
179-180, 183-184
1. Ar-O-CH_2- (169)
2. H_2O
Method A

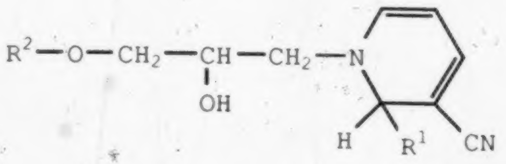
Ar= Ph, 1-naphthyl; R^1= n-Bu, t-Bu

Scheme 9. Synthetic routes used for the synthesis of 1-aryloxy-3-{1-[2-(or 6-alkyl)-3-cyano]-1,2- (or 1,6-)-dihydropyridyl}-2-propanols.

Table 7. Physical data for 1-aryloxy-3-{1-[2- (or 6-)alkyl-3-cyano-1,2- (or 1,6-)dihydropyridyl]}-2-propanols.



179-180, 183-184



181-182

Compd.	R^2	R^1	^{a}Isomer	Yield % Method A	Yield % Method B	^bR_f	Formula	Exact Mass Calcd.	Exact Mass Found	Microanalyses: Found (Calc.) C%	H%	N%
179	Ph	n-Bu	1,6	40	80	0.52	$C_{19}H_{24}N_2O_2$	312.1837	312.1834			
180^c	1-Naphthyl	n-Bu	1,6	42	-	0.60	$C_{23}H_{26}N_2O_2$	362.1994	362.1996	76.17	7.23	7.74
										(76.20)	(7.23)	(7.74)
181	Ph	t-Bu	1,2	-	78	0.55	$C_{19}H_{24}N_2O_2$	312.1837	312.1828	72.99	7.83	8.68
										(73.03)	(7.75)	(8.97)
182	1-Naphthyl	t-Bu	1,2	-	82	0.65	$C_{23}H_{26}N_2O_2$	(M-57)	(M-57)	75.77	7.41	7.59
							$C_{19}H_{17}N_2O_2$	305.1289	305.1281	(76.20)	(7.23)	(7.74)

Table 7. (cont.)

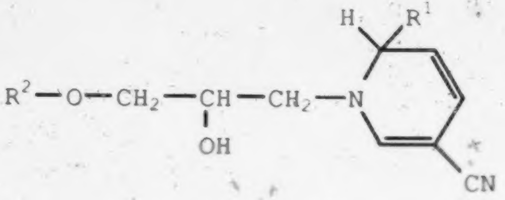
Compd.	R^2	R^1	[a]Isomer	Yield % Method A	Yield % Method B	[b]R_f	Formula	Exact Mass Calcd.	Exact Mass Found	Microanalyses: Found (Calc.) C%	H%	N%
183	Ph	t-Bu	1,6	-	76	0.52	$C_{19}H_{24}N_2O_2$	312.1837	312.1828	72.75	7.77	8.24
										(73.03)	(7.75)	(8.97)
184	1-Naphthyl	t-Bu	1,6	-	80	0.62	$C_{23}H_{26}N_2O_2$	362.1994	362.2010	75.81	7.64	7.22
										(76.20)	(7.23)	(7.74)

[a] All of the products existed as a mixture of two different diastereomers [RR(SS) and RS(SR)], as indicated by ^{1}H nmr spectrometry, in a ratio 1:1 except for (**180 and 183**) where the ratio was 1:2.

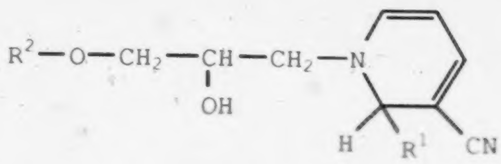
[b] Ether:hexane (7:3 v/v) as tlc development solvent.

[c] All of the products were oils except for compound (**180**) which was a light yellow solid, mp= 95 °C.

Table 8. Ir[a,b] and ^{1}H nmr[c] spectral data for 1-aryloxy-3-{1-[2-(or 6-)alkyl-3-cyano-1,2-(or 1,6-)dihydropyridyl]}-2-propanols.



179-180, 183-184



181-182

Comp.	ir (cm^{-1}) (OH)	(CN)	^{1}H nmr δ (ppm)
179	3410,	2193[a]	0.92 [t, J= 7 Hz, 3H, -(CH$_2$)$_3$-C$\underline{H}_3$]; 1.2-1.9 (m, 6H, -(C$\underline{H}_2$)$_3$-CH$_3$); 2.95 (br s, 1H, O$\underline{H}$, exchanges with deuterium oxide); 3.22-3.58 (m, 2H, -CH(OH)-C$\underline{H}_2$-DHP); 4.0 [m, 2H, -O-C$\underline{H}_2$-CH(OH)]; 4.16 (m, 2H, -CH$_2$-C$\underline{H}$(OH)-CH$_2$, DHP H-6); 5.04 and 5.06 (two d, $J_{4,5}$= 9.4 Hz of d, $J_{5,6}$= 5.0 Hz (ratio 1:1), 1H total, DHP H-5); 5.95 (d, $J_{4,5}$= 9.4 Hz, 1H, DHP H-4); 6.94 (m, 3H, *ortho*- hydrogens, DHP H-2); 7.04 (t, J= 7Hz, 1H, phenyl *para* -hydrogen); 7.35 (d, J= 7 Hz of d, J= 7 Hz, 2H, phenyl *meta* -hydrogens).

Table 8. (cont.)

180	3410, 2196[b]	0.90 [distorted t, J= 7 Hz, 3H, $-(CH_2)_3-C\underline{H}_3$]; 1.20-1.80 (m, 6H, $-(C\underline{H}_2)_3-CH_3$); 2.95 (br s, 1H, O$\underline{H}$, exchanges with deuterium oxide); 3.30-3.70 (m, 2H, $-CH(OH)-C\underline{H}_2-$DHP); 4.16 [m, 3H; $-O-C\underline{H}_2-CH(OH)-$, DHP H-6]; 4.30 [m, 1H, $-CH_2-C\underline{H}(OH)-$]; 5.04 and 5.05 (two d, $J_{4,5}$= 9.1 Hz of d, $J_{5,6}$= 5.2 Hz (ratio 1:2), 1H total, DHP H-5); 5.96 (d, $J_{4,5}$= 9.1 Hz, 1H, DHP H-4); 6.85 (d, J= 7.7 Hz, 1H, napthyl H-2); 6.95 and 6.97 (two s (ratio 1:2), 1H total, DHP H-2); 7.44 (t, J= 7.7 Hz, 1H, napthyl H-3); 7.5 (m, 3H, napthyl H-4, H-6, H-7); 7.88 (d, J= 7.7 Hz of d, J=2.1 Hz, 1H, napthyl H-8); 8.24 (d, J= 7.7 Hz of d, J=2.1 Hz, 1H, napthyl H-5).
181	3427; 2188[a]	0.94 (s, 9H, DHP t-Bu); 2.55 (br s, 1H, O$\underline{H}$, exchanges with deuterium oxide); 3.4-3.7 (m, 2H, $-CH(OH)-C\underline{H}_2-$DHP); 3.86 and 3.94 [two m, 2H total, $-O-C\underline{H}_2-CH(OH)$]; 3.92 (s, 1H, DHP H-2); 4.07 and 4.13 (two m (ratio 1:1), 1H total, $-CH_2-C\underline{H}(OH)-CH_2$); 4.96 and 4.97 (two d, $J_{4,5}$= 6.5 Hz of d, $J_{5,6}$= 6.5 Hz, 1H total, DHP H-5); 6.52 and 6.61 (two d, $J_{5,6}$= 6.5 Hz (ratio 1:1), 1H total, DHP H-6); 6.90 (m, 2H, phenyl *ortho* -hydrogens); 6.94 (d, $J_{4,5}$= 6.5 Hz, 1H, DHP H-4); 7.02 (d, J= 7.20 Hz of d, J= 7.20 Hz, 1H, phenyl *para* -hydrogen), 7.34 (d, J= 7.20 Hz of d, J= 7.20 Hz, 2H, J= 7.20 Hz, phenyl *meta* -hydrogens).

Table 8. (cont.)

182	3427, 2188^a	0.94 (s, 9H, DHP t-Bu); 2.8 (br s, 1H, O$\underline{H}$, exchanges with deuterium oxide); 3.42-3.76 (m, 2H, -CH(OH)-C$\underline{H}_2$-DHP); 3.93 (two d, $J_{2,6}$= 1.6 Hz (ratio 1:1), 1H total, DHP H-2); 4.10 [m, 2H, -O-C$\underline{H}_2$-CH(OH)]; 4.18 and 4.25 [two m (ratio 1:1), 1H total, C$\underline{H}$(OH) -CH$_2$]; 4.94 and 4.96 (two d, $J_{4,5}$= 5.4 Hz of d, $J_{5,6}$= 6.5 Hz (ratio 1:1), 1H total, DHP H-5); 6.52 and 6.62 (two d, $J_{5,6}$= 6.5 Hz of d, $J_{2,6}$= 1.6 Hz (ratio 1:1), 1H total, DHP H-6); 6.82 (d, J= 7.0 Hz, 1H, napthyl H-2); 6.88 and 6.90 (two d, $J_{4,5}$= 5.4 Hz (ratio 1:1), 1H total, DHP H-4); 7.4 (t, J= 7.0 Hz, 1H, napthyl H-3); 7.5 (d, J= 7.0 Hz, napthyl H-4); 7.5 (m, 2H, napthyl H-6, H-7); 7.84 (m, 1H, napthyl H-8); 8.26 (m, 1H, napthyl H-5).
183	3410, 2196^a	0.89 and 0.9 [two s (ratio 2:1), 9H total, DHP t-Bu]; 2.66 (br s, 1H, O$\underline{H}$, exchanges with deuterium oxide); 3.46-3.68 (m, 2H, -CH(OH)-C$\underline{H}_2$-DHP); 3.76 and 3.80 [two d, $J_{5,6}$= 6.2 Hz of d, $J_{2,6}$= 1.4 Hz (ratio 1:2), 1H total, DHP H-6]; 3.96 [m, 2H, -O-C$\underline{H}_2$]; 4.10 (m, 1H, -CH$_2$-C$\underline{H}$(OH)-CH$_2$); 5.02 and 5.05 (two d, $J_{4,5}$= 9.4 Hz of d, $J_{5,6}$= 6.2 Hz (ratio 1:2), 1H total, DHP H-5); 6.12 (d, $J_{4,5}$= 9.4 Hz, 1H, DHP H-4); 6.93 (d, J= 8.6 Hz, 2H, phenyl *ortho* -hydrogens); 7.01 and 7.03 [two s (ratio 1:2), 1H total, DHP H-2];

Table 8. (cont.)

		7.01(m, 1H, phenyl *para* -hydrogen); 7.34 (t, J= 8.60 Hz, 2H, phenyl *meta* -hydrogens).
184	3410, 2196[a]	0.90 and 0.92 [two s (ratio 2:1), 9H total, DHP t-Bu]; 2.85 (br s, 1H, O$\underline{H}$ exchanges with deuterium oxide); 3.44-3.70 (m, 2H, -CH(OH)-C$\underline{H}_2$-DHP); 3.76 and 3.79 [two d, $J_{5,6}$= 6.1 Hz of d, $J_{2,6}$= 1.4 Hz (ratio 1:1), 1H total, DHP H-6]; 4.10 [m, 2H, -O-C$\underline{H}_2$-CH(OH)-]; 4.20 [m, 1H, -CH$_2$-C$\underline{H}$(OH)-CH$_2$]; 4.92 and 4.96 (two d, $J_{4,5}$= 9.5 Hz of d, $J_{5,6}$= 6.1 Hz, 1H total, DHP H-5); 6.06 (d, $J_{4,5}$= 9.5 Hz, 1H, DHP H-4); 6.8 (d, J= 8.1 Hz, 1H, napthyl H-2); 7.0 and 7.02 [two d, $J_{2,6}$= 1.4 Hz (ratio 1:1), 1H total, DHP H-2]; 7.40 (dd, J= 8.1 Hz, 1H, napthyl H-3); 7.52 (m, 3H, napthyl H-4, H-6, H-7); 7.85 (m, 1H, napthyl H-8); 8.2 (m, 1H, napthyl H-5).

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[a] Film

[b] KBr

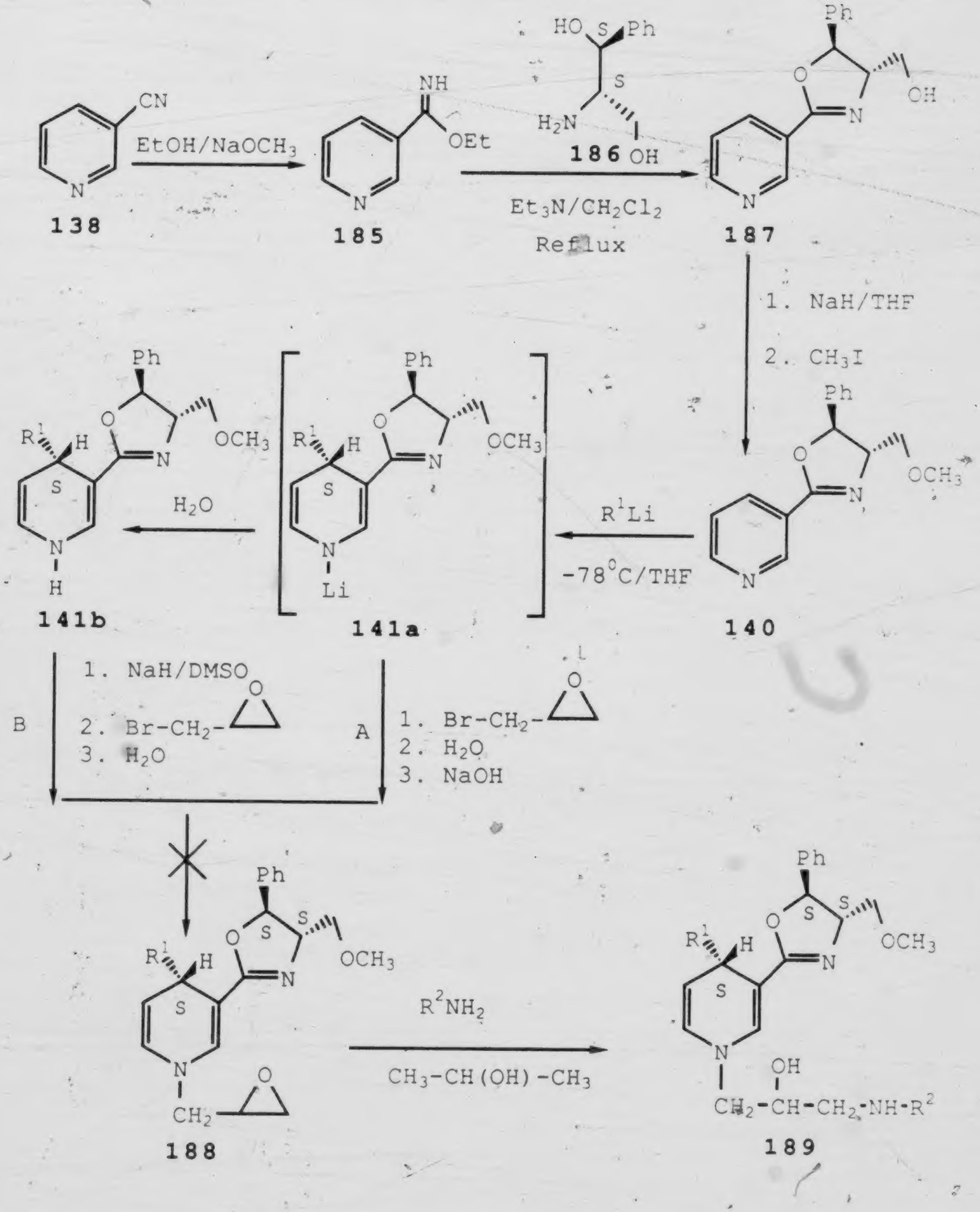
[c] CDCl$_3$

3.3.0.0.0 SYNTHESIS OF 1-{1-[4-(S)-ALKYL(ARYL)-3-[4-(S)-METHOXYMETHYL-5-(S)-PHENYLOXAZOLIN-2-YL]-1,4-DIHYDROPYRIDYL}-3-ALKYLAMINO-2-PROPANOLS.

A study to replace the aryloxy moiety of class B aryloxypropanolamines, by a chiral 1,4-dihydropyridine ring system that is stablized by an electron-attracting 3-[4-(S)-methoxymethyl-5-(S)-phenyloxazolin-2-yl] substituent was initiated to investigate the effect which a C-4 chiral center in a 1,4-dihydropyridyl ring system has upon β-adrenergic antagonist activity (see structure **189**). The syntheses of (+)-4-(S)-alkyl(aryl)-3-(oxazolin-2-yl)-1,4-dihyhydropyridines (**141b**) under acid conditions have been reported[441-443] using the procedures illustrated in Scheme 3. Since low yields were obtained using this method, and the mixture of imidate salt (**139**) and quarternized pyridine salt (**138**) were difficult to separate, the alternative synthetic method outlined in Scheme 10 was used to synthesize (**185**) under alkaline reaction conditions[448]. The reaction of 3-cyanopyridine (**138**) with absolute ethanol in the presence of $NaOCH_3$ at room temperature for three days afforded (**185**) in 70% yield together with unreacted (**138**) which were separated by distillation (60 °C, 20 mm Hg). Subsequently, compound (**187**) was prepared in 70% yield by heating a solution of the imidate (**185**), 1.0 equivalent of triethylamine in dry 1,2-dichloromethane, and 1.0 equivalent of the (+)-aminodiol (**186**) at reflux for 16 h. The mp and optical rotation for (**187**) were 125-126 °C and $[\alpha]_D^{23} = -34.36$ (c 0.40, $CHCl_3$), respectively. The literature values[443] were mp 124-125 °C and $[\alpha]_D^{23} = -33.30$ (c 10.5, $CHCl_3$) respectively. Reaction of (**187**) with NaH/CH_3I in THF afforded (**140**) as a pure liquid in 95% yield. The optical rotation for (**140**) was $[\alpha]_D^{23} = +44.16$ (c 0.60, $CHCl_3$), relative to the literature value[443] of $[\alpha]_D^{23}$= +42.70 (c 0.60, $CHCl_3$). The physical data, and the ^1H nmr and ir spectroscopic data for (**187** and **140**) are presented in experimental section 6.1.0.0.0. Addition of an alkyl(aryl)organolithium reagent to (**140**) in THF at -78 °C followed by hydrolysis with water afforded (**141b**). Since compound (**141b**) was unstable at room temperature, the direct reaction of (**141a**) with epibromohydrin was used (method A) for the synthesis of (**188**). Compound (**188**) was very unstable. Further attempts to synthesize (**189**) by reaction of (**188**) with isopropylamine or t-butylamine as illustrated in Scheme 10 were unsuccessful.

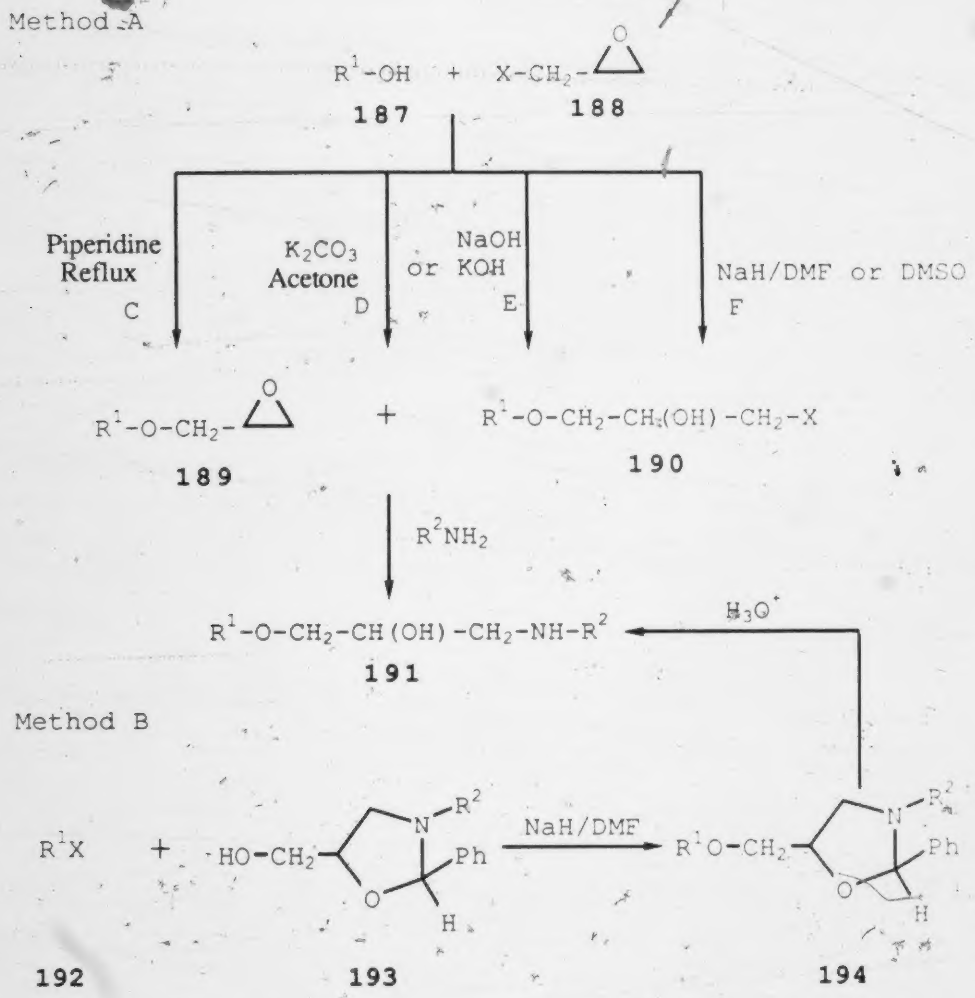
3.4.0.0.0 GENERAL METHODS FOR THE SYNTHESIS OF HETEROARYLOXY-PROPANOLAMINES.

Most β-blocking agents in current clinical use are class B aryloxypropanolamines. Following the discovery of propranolol and related aryloxypropanolamines, most investigations to design new β-blockers have involved primarily class B compounds. The procedure that is generally used to prepare heteroaryl(aryl)oxypropanolamines involves the reaction of an epihalohydrin (**188**) with a heteroaryl or aryl alcohol (**187**) by four different procedures (C[446], D[448], E[449] and F[450]). Procedures C and D afforded both **189** and **190**. Procedures E and F yield **189** as the major product. The intermediate chlorohydrin (**190**) or epoxide (**189**), which is usually not isolated, was reacted immediately with the appropriate amine to afford the corresponding heteroaryl-(aryl)oxypropanolamine (**191**) as outlined in Scheme 11 method A.


138
EtOH/NaOCH3
185
NH
OEt
HO S Ph
S
H2N
186
OH
Et3N/CH2Cl2
Reflux
187
Ph
O
N
OH
1. NaH/THF
2. CH3I
140
OCH3
R1Li
-78°C/THF
141a
Li
H2O
141b
R1
H
S
B
1. NaH/DMSO
2. Br-CH2-
3. H2O
A
1. Br-CH2-
2. H2O
3. NaOH
188
CH2
R2NH2
CH3-CH(OH)-CH3
189
CH2-CH-CH2-NH-R2

R^1= Ph, n-Bu ; R^2= $CH(CH_3)_2$, $C(CH_3)_3$

Scheme 10. Synthetic routes for the attempted preparation of 1-{1-[4-(S)-alkyl(aryl)-3-[4-(S)-methoxymethyl-5-(S)-phenyloxazolin-2-yl)]-1,4-dihydropyridyl}-3-alkylamino-2-propanol (**189**).

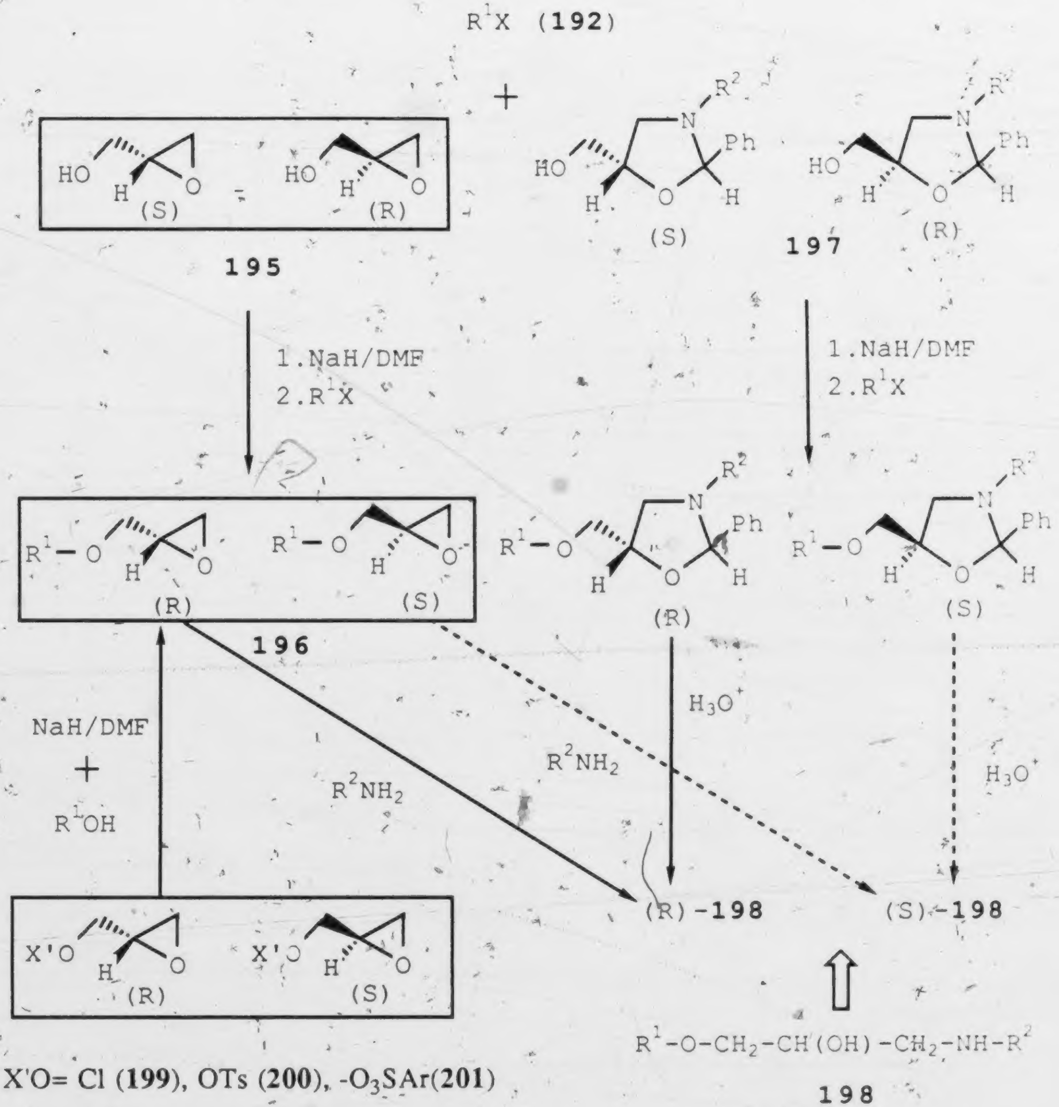

Method A
R1-OH + X-CH2-
187
188
Piperidine Reflux
C
K2CO3 Acetone
D
NaOH or KOH
E
NaH/DMF or DMSO
F
R1-O-CH2-
189
+
R1-O-CH2-CH(OH)-CH2-X
190
R2NH2
R1-O-CH2-CH(OH)-CH2-NH-R2
191
H3O+
Method B
R1X
192
HO-CH2-
N
R2
Ph
O
H
193
NaH/DMF
R1O-CH2-
194

R^1= Heterocyclic ring

Scheme 11. General method for the synthesis of heteroaryloxypropanolamines.

Procedure F offers advantages over procedures C and D, since the former procedure uses stoichiometric amounts of the highly toxic epihalohydrin, provides higher chemical yields and cleaner reactions than procedures C, D and E. Procedure F was therefore utilized for the synthetic studies described in this thesis.

Another common method used to synthesize (**191**) involves the reaction of a heteroaryl halide (**192**) with 5-hydroxymethyl-2-phenyl-1,3-oxazolidine (**192**)[451] in a suspension of NaH in DMF as illustrated in Scheme 11 method B. Several approaches to the synthesis of chiral heteroaryloxypropanolamines (**191**) have been developed. The most direct method involves the reaction of a heteroaryl reagent bearing a facile leaving group (**192**) with the sodium salt of a chiral glycidol[451] to afford chiral heteroaryloxymethyloxiranes (**196**). Further reaction of (R)- or (S)-(**196**) with appropriate amines yielded chiral heteroaryloxy propanolamines (**198**) with retention of configuration as reported[452]. Compounds (**198**) were also synthesized by the reaction of (**192**) with a chiral (R- or S-)-5-hydroxymethyl-2-phenyl-1,3-oxazolidine[452] in the presence of sodium hydride in DMF (see Scheme 12). Alternative procedures involve the reaction of a chiral epichlorohydrin (**199**),[453] chiral glycidyl tosylate (**200**)[454] or glycidyl arensulfonate (**201**)[455] with the preformed phenoxide of (**187**) in DMF to yield a chiral heteroaryloxymethyloxirane (**196**). The subsequent reaction of (**196**) with selected amines afforded the corresponding chiral heteroaryloxy-propanolamine (**198**)[452] as illustrated in Scheme 12.



R^1X (**192**)
+
HO
H
O
(S)
(R)
195
R^2
N
Ph
HO
H
O
H
(S)
(R)
197
1.NaH/DMF
2.R^1X
1.NaH/DMF
2.R^1X
R^1—O
(R)
(S)
196
NaH/DMF
+
R^1OH
R^2NH_2
R^2NH_2
H_3O^+
H_3O^+
(R)-**198**
(S)-**198**
X'O
(R)
(S)
R^1-O-CH_2-CH(OH)-CH_2-NH-R^2
198

X'O= Cl (**199**), OTs (**200**), -O_3SAr(**201**)

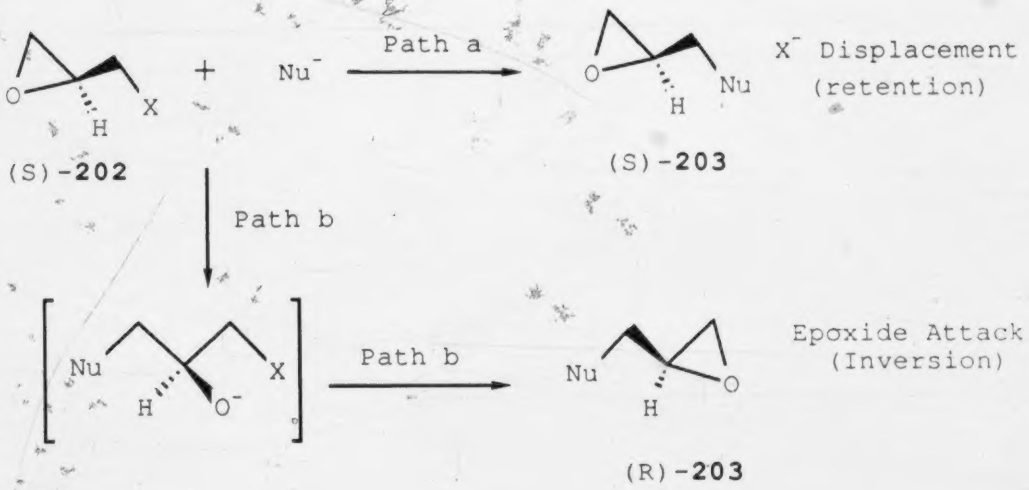
Scheme 12. General method for the synthesis of chiral heteroaryloxypropanolamines.

3.4.1.0.0 SYNTHESIS OF 1-(QUINOLYLOXY)-3-(ALKYLAMINO)PROPAN-2-OL.

Quinoline, which is an isostere of naphthalene, is present in a large number of compounds that exhibit a wide spectrum of biological activities[456]. It was therefore of interest to replace the nahpthyl ring of propranolol (**7**) by a 2-, 4- or 5-quinolyl moiety and the N-alkylamino group by selected cycloalkyl or arylalkyl groups to determine the effect of these replacements upon β-adrenergic antagonist activity.

3.4.1.1.0 SYNTHESIS OF RACEMIC AND CHIRAL 1-(QUINOL-5-YLOXY)-2,3-EPOXYPROPANES.

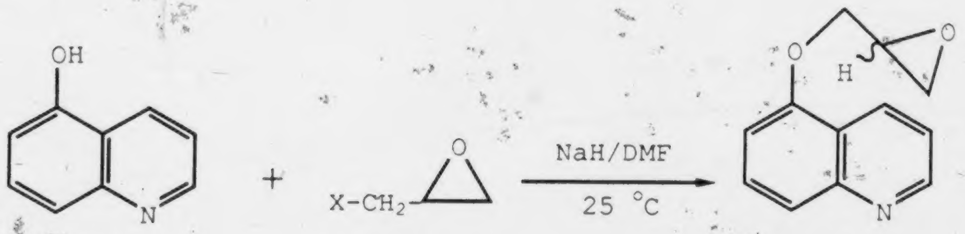
McClure and co-workers[448] have investigated regioselectivity for reactions of optical active glycidol derivatives (**202**) with aryloxide nucleophiles. This study showed a substantial loss in optical purity when the leaving group X (**202**) was a chloro or mesylate substituent (Scheme 13). Since the configuration of the products produced using an optically enriched oxirane (**202**) according to path a or b in Scheme 13 would not be identical, the determination of the absolute configuration and chiral purity of (**203**) would establish the mode of nucleophilic substitution. In other investigations, the reaction of (2S)-glycidyl tosylate with different preformed aryloxides in DMF, prepared using NaH as base, indicated that the formation of aryloxymethyloxiranes (**203**) occurred with retention of configuration[454,455]. In addition, sodium or potasium hydroxide could be used with no decrease in regioselectivity[455].


Path a
X⁻ Displacement
(retention)
(S)-202
(S)-203
Path b
Path b
Epoxide Attack
(Inversion)
(R)-203
Nu⁻
Nu
X
O
H

X= Cl; OMs; OTf.

Scheme 13. Mechanism of nucleophilic addition to epichlorohydrin and related species: Chiral aryloxymethyloxiranes (**203**).

This method was used to prepare (R,S), (R)- and (S)-1-(quinol-5-yloxy)-2,3-epoxypropanes by reaction of the preformed sodium salt of 5-hydroxyquinoline (**204**) in DMF at 25 $^{\circ}C$ with (R,S)-epibromohydrin (**205**), (2R)-glycidyl tosylate $[\alpha]_D^{19} = -17^{\circ}$ (c= 2.75, $CHCl_3$) (**206**) or (2S)-glycidyl tosylate $[\alpha]^{19} = +17^{\circ}$ (c= 2.75, $CHCl_3$) (**207**). The respective products (R,S) (**208**), (R)-(**209**) and (S)-1-(quinol-5-yloxy)-2,3-epoxypropane (**210**) obtained were purified by column chromatography to provide 80-83% isolated chemical yields as shown in Scheme 14.



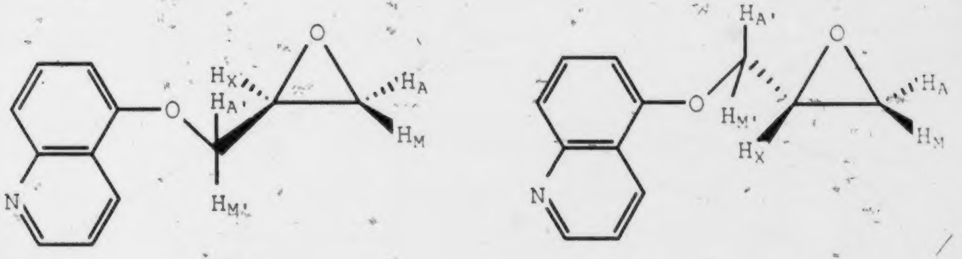
204

205 X= Br
206 X= (2R)-Tosylate
207 X= (2S)-Tosylate

208
209
210

Scheme 14. The synthesis of (R,S), (R)- and (S)-1-(quinol-5-yloxy)-2,3-epoxypropanes (**208-210**)

The physical data for (**208-210**) are shown in Table 9 and ^{1}H nmr and ir spectroscopic data are summarized in Table 10. The ir spectra of oxiranes (**208-210**) exhibit three intense bands at 1271 (aromatic C-O ether), 1250, 1180 (oxirane C-O ether), and 805 cm^{-1}.[458,459] The latter band at 805 cm^{-1} is due to the asymmetrical stretching vibration for the oxirane ring[459]. The absorption band at 3066 cm^{-1} is due to the aromatic protons and that at 1614 cm^{-1} is due to an aromatic C=C stretching vibration. An examination of the ^{1}H nmr spectra of (**208-210**) indicated that the C-1 and C-3 methylene protons were chemically and magnetically nonequivalent appearing as a typical AMX pattern as illustrated by the structures in Figure 11. Generally, the two C-3 protons appeared as one quartet centered at δ 2.85-2.86 (J_{gem}= 4.23-4.60 Hz and J_{vic}= 2.42-3.29 Hz), a triplet at δ 3.0 for H_M (J_{gem}= J_{vic}= 4.23-4.60 Hz). The two C-1 protons ($H_{A'}$ and $H_{M'}$) appeared as a pair of quartets at 4.14 δ (J_{gem}= 10.82-11.15 Hz and J_{vic}= 5.64-5.80 Hz) for $H_{A'}$ and at δ 4.47-4.48 (J_{gem}= 10.82-11.15 Hz and J_{vic}= 2.40-1.91 Hz) for $H_{M'}$.



(S)-**210**

(R)-**209**

Figure 11. A typical AMX coupling spin system for (R)- and (S)-1-(quinol-5-yloxy)-2,3-epoxypropanes (**209-210**).

Cis-Vicinal coupling constants for oxiranes are generaly larger than the corresponding *trans*-coupling constants.[460] Thus the ^1H nmr spectra showed that J_{AX}= 3.29 Hz [(R)-**209**] > J_{AX}= 2.42 Hz [(S)-**210**].

The optical rotations of (R)-**209** and (S)-**210** were calculated using the equation illustrated below:

$$[\alpha]_D^{T^\circ} = \frac{\alpha}{l \times d}$$

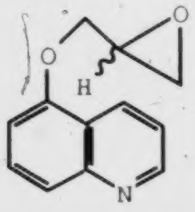
$$\text{specific rotation} = \frac{\text{observed rotation (degrees)}}{\text{length (dm)} \times \text{g/cc}}$$

where d represents density or concentration of (**209** and **210**) using chloroform ($CHCl_3$) as solvent, T° is the temperature (23°C) and D is the wavelength of light used in the measurement (D line of sodium, 5893 Å). The measurement was performed three times for each compound using different tube lengths (l= 1.0 and 2.0 dm) at different concentrations. The optical rotation for (R)-**209** was $[\alpha]_D^{23}$ = -27.27° (c = 0.01, $CHCl_3$)

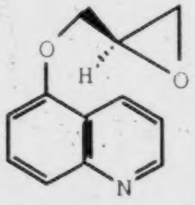
while that for (S)-**210** was $[\alpha]_D^{23} = +27.27^o$ (c = 0.01, $CHCl_3$) (see Table 9).

The enantiomeric purity of these products was determined by acquisition of ^1H nmr (δ) spectra for (**209-210**) in the presence of a chiral shift reagent (CSR), $Eu(hfbc)_3$ {tris [3-heptafluorobutyryl-d-camphorato]-europium}[458,455]. The information presented in Table 11 indicates that the 1H triplet at δ 3.0 assigned to H_M for racemic (**208**) is resolved into two multiplets at δ 3.16 and 3.18 with a 1:1 ratio in the presence of 3.0×10^{-5} M CSR. Increasing the concentration of the CSR to 6.0×10^{-5} M results in a further deshielding effect where the H_M resonances appeared at δ 3.33 and 3.38. When the concentration of CSR is 3.0×10^{-5} M or higher, the initial 1H triplet at δ 3.0 assigned to H_M in the absence of CSR, for both (R)-**209** and (S)-**210**, collapsed to a singlet and is shifted to lower field. This indicates that the purity of (R)-**209** or (S)-**210** can be estimated at a number of concentrations of CSR greater than 3.0×10^{-5} M. However, when the same concentration of CSR is employed, the protons in (R)-**209** are deshielded more than the corresponding proton in (S)-**210** shown in Table 11.

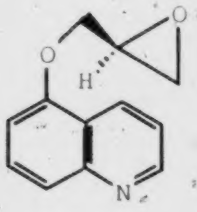
Table 9. Some physical data for (2R,2S)-, (2R)- and (2S)-1-(quinol-5-yloxy)-2,3-epoxypropanes (**208-210**).



(2R,2S)-**208**



(2R)-**209**



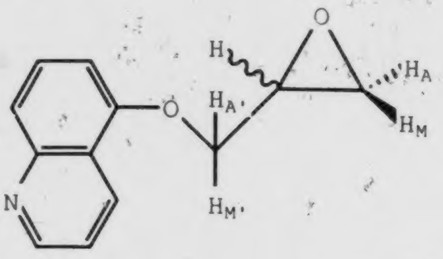
(2S)-**210**

Compd.	R_f[a]	mp°C	Yield, %	Configuration	Optical rotation $[\alpha]_D^{23}$	Formula	Microanalysies: Found (Calcd.) %C	%H	%N
208	0.55	48	80	R,S	0	$C_{12}H_{11}NO_2$	ND[b]		
209	0.62	78	80	R	-27.27	$C_{12}H_{11}NO_2$	ND[b]		
210	0.62	78	83	S	+27.27	$C_{12}H_{11}NO_2$	71.79 (71.62)	5.31 (5.51)	6.86 (6.96)

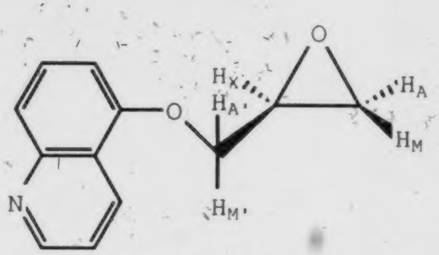
[a] Ether as development solvent.

[b] ND= not determined.

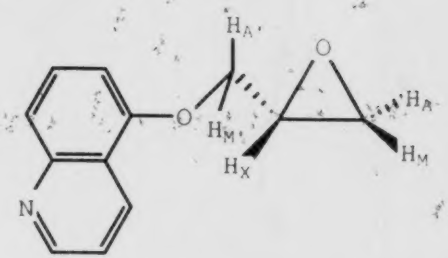
Table 10. Ir[a] and ^{1}H nmr[b] spectral data for (2R,2S)-, (2R)- and (2S)-1-(quinol-5-yloxy)-2,3-epoxypropanes (**208-210**).



(2R,2S)-**208**



(2S)-**210**



(2R)-**209**

Compd.	ir (cm^{-1})		^{1}H nmr δ (ppm)
	(aromatic C-H)	(epoxide C-O)	
208	3066	1250	2.85 (d, J_{vic}= 2.42 Hz of d, J_{gem}= 4.36 Hz, 1H, H_A); 3.0 (d, J_{vic}= 4.36 Hz of d, J_{gem}= 4.36 Hz, 1H, H_M); 3.52 (m, 1H, H_X); 4.14 (d, J_{vic}= 5.80 Hz of d, J_{gem}= 11.15 Hz, 1H, $H_{A'}$); 4.47 (J_{vic}= 2.91 Hz of d, J_{gem}= 11.15 Hz, 1H, $H_{M'}$); 6.89 (d, $J_{6,7}$= 8.26 Hz, 1H, quinolyl H-6); 7.42 (d, $J_{3,4}$= 8.26 Hz of d, $J_{2,3}$= 4.72 Hz, 1H, quinolyl H-3); 7.63 (t, $J_{6,7}$= $J_{7,8}$= 8.26 Hz, 1H, quinolyl H-7); 7.76 (d, $J_{7,8}$= 8.26

Table 10. (cont.)

			Hz, 1H, quinolyl H-8); 8.66 (d, $J_{3,4}$= 8.26 Hz of d, $J_{2,4}$= 2.36 Hz, 1H, quinolyl H-4); 8.94 (d, $J_{2,3}$= 4.72 Hz of d, $J_{2,4}$= 2.36 Hz, 1H, quinolyl H-2).
209	3066	1250	2.86 (d, J_{vic}= 3.29 Hz of d, J_{gem}= 4.23 Hz, 1H, H_A); 3.0 (dd, J_{vic}= J_{gem}= 4.23 Hz, 1H, H_M); 3.52 (m, 1H, H_X); 4.14 (d, J_{vic}= 5.64 Hz of d, J_{gem}= 10.82 Hz, 1H, $H_{A'}$); 4.47 (J_{vic}= 2.82 Hz of d, J_{gem}= 10.82Hz, 1H, $H_{M'}$); 6.88 (d, $J_{6,7}$= 7.95 Hz, 1H, quinolyl H-6); 7.42 (d, $J_{3,4}$= 7.95 Hz of d, $J_{2,3}$= 4.52 Hz, 1H, quinolyl H-3); 7.63 (t, J 6,7= $J_{7,8}$= 7.95 Hz, 1H, quinolyl H-7); 7.75 (d, $J_{7,8}$= 7.95 Hz, 1H, quinolyl H-8); 8.65 (d, $J_{3,4}$= 7.95 Hz of d, $J_{2,4}$= 1.69 Hz, 1H, quinolyl H-4); 8.92 (d, $J_{2,3}$= 4.52 Hz of d, $J_{2,4}$= 1.69 Hz, 1H, quinolyl H-2).
210	3066	1250	2.86 (d, J_{vic}= 2.42 Hz of d, J_{gem}= 4.60 Hz, 1H, H_A); 3.00 (d, J_{vic}= 4.60 Hz of d, J_{gem}= 4.6 Hz, 1H, H_M); 3.52 (m, 1H, H_X); 4.14 (d, J_{vic}= 5.85 Hz of d, J_{gem}= 11.5 Hz, 1H, $H_{A'}$); 4.48 (J_{vic} = 2.40 Hz of d, J_{gem}= 11.15 Hz, 1H, $H_{M'}$); 6.9 (d, $J_{6,7}$= 8.0 Hz, 1H, quinolyl H-6); 7.43 (d, $J_{3,4}$= 8.0 Hz of d, $J_{2,3}$= 4.6 Hz, 1H, quinolyl H-3); 7.64 (d, $J_{6,7}$= 8.0 Hz of d, $J_{7,8}$= 8.0 Hz, 1H, quinolyl H-7); 7.76 (d, $J_{7,8}$= 8.0 Hz,

Table 10. (cont.)

1H, quinolyl H-8); 8.66 (d, $J_{3,4}$= 8.0 Hz of d, $J_{2,4}$= 2.3 Hz, 1H, quinolyl H-4); 8.95 (d, $J_{2,3}$= 4.6 Hz of d, $J_{2,4}$= 2.3 Hz, 1H, quinolyl H-2).

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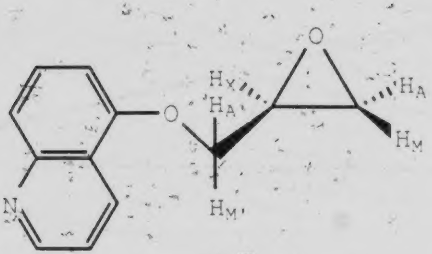
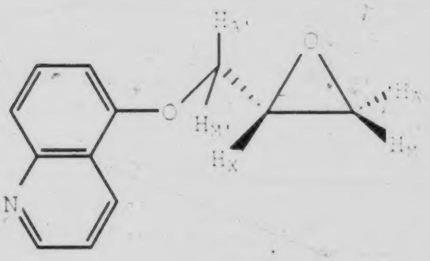
[a] KBr

[b] $CDCl_3$



(S)-**210**



(R)-**209**

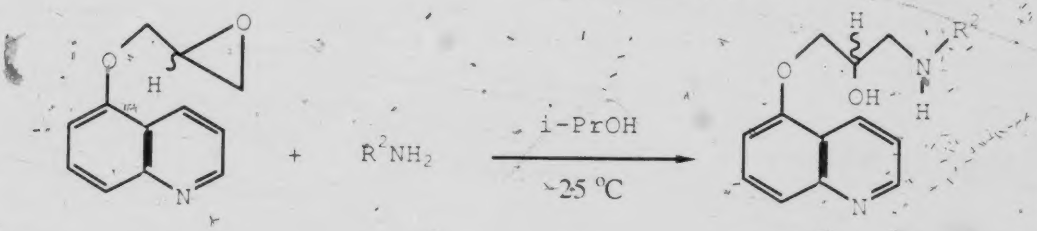
			Chemical shift δ (ppm)		
[a]Comp.	[b]CSR	Configuration	H_A	H_M	H_X
208	0	Racemate	2.85	3.00	3.52
	3.0×10^{-5}	Racemate	3.06	3.16 and 3.18	3.75
	6.0×10^{-5}	Racemate	3.24	3.33 and 3.38	3.94
	9.0×10^{-5}	Racemate	3.40	3.50	4.12
	12.0×10^{-5}	Racemate	3.55	3.60	4.25
209	0	R	2.86	3.00	3.52
	3.0×10^{-5}	R	3.40	3.46	4.14
	6.0×10^{-5}	R	3.79	3.85	4.60
	9.0×10^{-5}	R	4.10	4.15	4.91
210	0	S	2.86	3.00	3.52
	3.0×10^{-5}	S	3.08	3.20	3.75
	6.0×10^{-5}	S	3.30	3.40	3.98
	9.0×10^{-5}	S	3.46	3.56	4.16
	12.0×10^{-5}	S	3.64	3.72	4.32

[a]concentration of compound = 1.0×10^{-1} M, [b]Concentration of CSR.

Table 11. Chemical shifts, ^1H nmr (δ) ppm for (R,S)-, (R)- and (S)-1-(quinol-5-yloxy)-2,3-epoxypropanes in the presence of CSR.

3.4.1.2.0 SYNTHESIS OF (R,S)-1-(QUINOL-5-YLOXY)-3-ALKYLAMINO-2-PROPANOLS.

Reaction of racemic (**208**) with 2 to 4 equivalents of isopropylamine, t-butylamine or cyclohexylamine in 2-propanol at room temperature for 24-36 h, and recrystallization of the respective product from ether:hexane afforded (**211-213**) in 90-96 % yield (see Scheme 15).



(R,S)-**208** (**R,S)-211-213**

211 R^2= $-CH(CH_3)_2$, **212** R^2= $-C(CH_3)_3$, **212** R^2= cyclohexyl.

Scheme 15. The synthesis of (R,S)-1-(quinol-5-yloxy)-3-isopropyl, (t-butyl or cyclohexyl)amino-2-propanols.

The physical data for (**211-213**) are presented in Table 12, and the ^{1}H nmr (δ) and ir spectroscopic data are summarized in Table 13. Compounds (**211-213**), which possess one chiral center, are racemates. Examination of the ^{1}H nmr spectra for compounds (**211-213**) indicated that the oxygen methylene protons ($O-CH_2-$) exhibited the same chemical shift. In contrast the methylene protons attached to the isopropyl, t-butyl or cyclohexylamino groups were chemically and magnetically non-equivalent. The ir spectra (cm^{-1}) for compounds (**211-213**) exhibited absorptions at 1617-1622 (C=N), 1264-1268 (aromatic-C-O), 1172-1175 (aliphatic-C-O) and 1140-1096 (alcohol C-O stretching vibration). The NH absorption for (**211**,**212**) coincided with the OH absorptions at 3230 cm^{-1} and was present at 3264 cm^{-1} for (**213**). The strong hydrogen bonding absorptions at 3066-3262 (OH) are illustrated in Figure 12.

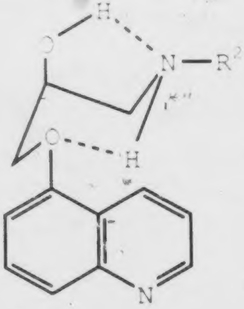
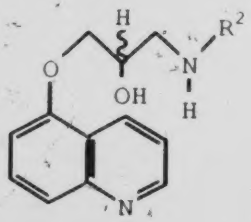


Figure 12. The hydrogen bonding absorptions of OH for (**211-213**).

The strength of hydrogen bonding is dependent upon the electron density on N which is determined by the electron donating (+I) and steric effects of the R^2-substituent. The relative strength of the hydroxyl hydrogen bond for compounds (**211-213**) is cyclohexyl < isopropyl < t-butyl which give rise to the absorptions at 3066, 3230 and 3262, respectively.

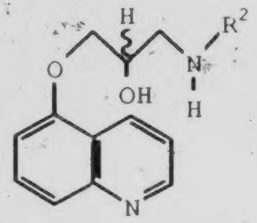
Table 12. Physical data for (2R,2S)-1-(quinol-5-yloxy) -3-isopropyl(t-butyl or cyclohexyl)amino-2-propanols.



(2R,2S)-211-213

Compd.	R^2	Reaction Time (h)	Yield,%	MP,^oC	Formula	Microanalyses: Found (Calcd.) %C	 %H	 %N
211	$CH(CH_3)_2$	24	90	60	$C_{15}H_{20}N_2O_2$	69.08	7.84	10.68
						(69.19)	(7.74)	(10.76)
212	$C(CH_3)_3$	36	96	39	$C_{16}H_{22}N_2O_2$	70.22	8.28	10.04
						(70.03)	(8.08)	(10.21)
213	Cyclohexyl	36	96	116	$C_{18}H_{24}N_2O_2$	71.68	8.08	9.44
						(71.96)	(8.05)	(9.32)

Table 13. Ir[a] and ^{1}H nmr[b] spectral data for (2R,2S)-1-(quinol-5-yloxy)-3-isopropyl(t-butyl or cyclohexyl)amino-2-propanols.



(2R,2S)-211-213

R^2= $CH(CH_3)_2$, $C(CH_3)_3$, cyclohexyl

Compd.	ir (cm^{-1})(OH)	^{1}H nmr δ (ppm)
211	3230	1.1 (d, J= 6.56 Hz, 6H, -NH-CH($\underline{CH_3}$)$_2$; 2.0 (br s, 2H, -$\underline{NH}$ and -$\underline{OH}$ exchange with deuterium oxide); 2.84 [m, 2H, -CH(OH)-C$\underline{H}$H^1-NH-, -NH-$\underline{CH}$(CH$_3$)$_2$]; 3.0 (d, J_{vic}= 3.78 Hz of d, J_{gem}= 12.28 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-); 4.16 [m, 2H, -O-$\underline{CH_2}$-CH(OH)-]; 4.23 (m, 1H, -CH$_2$-$\underline{CH}$(OH)-CH$_2$-NH-); 6.84 (d, $J_{6,7}$= 8.4 Hz, 1H, quinolyl H-6); 7.30 (d, $J_{3,4}$= 8.96 Hz of d, $J_{2,3}$= 4.48 Hz, 1H, quinolyl H-3); 7.56 (d, $J_{6,7}$= 8.4 Hz of d, $J_{7,8}$= 8.4 Hz, 1H, quinolyl H-7); 7.72 (d, $J_{7,8}$= 8.4 Hz, 1H,

Table 13. (cont.)

		quinolyl H-8); 8.53 (d, $J_{3,4}$= 8.96 Hz of d, $J_{2,4}$= 1.68 Hz, 1H, quinolyl H-4); 8.88 (d, $J_{2,3}$= 4.48 Hz of d, $J_{2,4}$= 1.68 Hz, 1H, quinolyl H-2).
212	3262	1.15 (s, 9H, -NH-C$(\underline{CH}_3)_3$; 2.80 (d, J_{vic}= 7.76 Hz of d, J_{gem}= 11.64 Hz, 1H, -CH(OH)-C$\underline{H}$H^1-NH-); 2.98 (J_{vic}= 3.38 Hz of d, J_{gem}= 11.64 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-); 3.5 (br s, 2H, -$\underline{NH}$ and -$\underline{OH}$, exchange with deuterium oxide); 4.19 [m, 3H, -O-$\underline{CH}_2$-CH(OH)- , -CH$_2$-$\underline{CH}$(OH)-]; 6.90 (d, $J_{6,7}$= 8.12Hz, 1H, quinolyl H-6); 7.38 (d, $J_{3,4}$= 8.7 Hz of d, $J_{2,3}$= 4.64 Hz, 1H, quinolyl H-3); 7.62 (d, $J_{6,7}$= 8.12 Hz of d, $J_{7,8}$= 8.12 Hz, 1H, quinolyl H-7); 7.74 (d, $J_{7,8}$= 8.12 Hz, 1H, quinolyl H-8); 8.59 (d, $J_{3,4}$= 8.7 Hz of d, $J_{2,4}$= 1.2 Hz, 1H, quinolyl H-4); 8.93 (d, $J_{2,3}$= 4.64 Hz of d, $J_{2,4}$= 1.2 Hz, 1H, quinolyl H-2).
213	3246	1.01-2.04 (m, 10H, cyclohexyl hydrogens); 2.48 [m, 1H, -NH-$\underline{CH}$(cyclohexyl)]; 2.62 (br s, 2H, -$\underline{NH}$, -$\underline{OH}$ exchange with deuterium oxide); 2.85 (m, 1H, -C$\underline{H}$H^1-NH-); 3.06 (d, J_{vic}= 4.0 Hz of d, J_{gem}= 12.0 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-); 4.18 (m, 3H, -O-$\underline{CH}_2$-CH(OH)- , -CH$_2$-$\underline{CH}$(OH)-]; 6.88 (d, $J_{6,7}$= 8.25 Hz, 1H, quinolyl H-6); 7.38 (d, $J_{3,4}$= 8.25 Hz of d, $J_{2,3}$= 4.25 Hz, 1H, quinolyl H-3); 7.6 (d, $J_{6,7}$= 8.25 Hz of d,

Table 13. (cont.)

$J_{7,8}$= 8.25 Hz, 1H, quinolyl H-7); 7.72 (d, $J_{7,8}$= 8.25 Hz, 1H, quinolyl H-8); 8.58 (d, $J_{3,4}$= 8.25 Hz of d, $J_{2,4}$= 1.50 Hz, 1H, quinoliyl H-4); 8.90 (d, $J_{2,3}$= 4.50 Hz of d, $J_{2,4}$= 1.50 Hz, 1H, quinolyl H-2).

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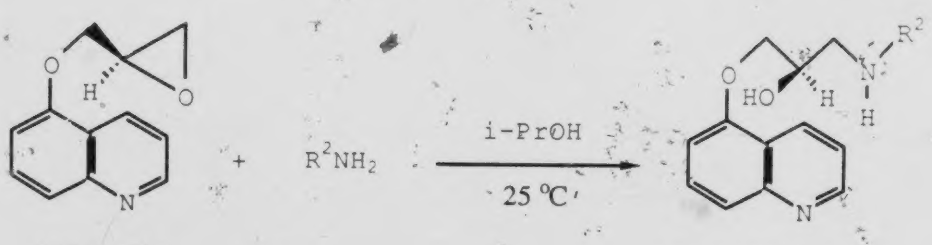
[a] KBr

[b] $CDCl_3$

3.4.1.3.0 SYNTHESIS OF (2R)-1-(QUINOL-5-YLOXY)-3-ALKYLAMINO-2-PROPANOLS.

Reaction of (-)-(R)-1-(quinol-5-yloxy)-2,3-epoxypropane **(209)** with isopropylamine or t-butylamine in 2-propanol at 25 °C for 24-36 h, afforded the respective free bases (**214-215**) as oils. Dissolution of each free base in dry ether, treatment with anhydrous HCl gas until no further precipitation of (**214-215**) was observed, followed by recrystallization from absolute ethyl alcohol yielded (**214** and **215**), respectively as the 2HCl salts in 95-96% yield as outlined in Scheme 16. Compounds (**214-215**) were predicted to have the same configuration as the epoxide configuration (**209**) as illustrated in literature[452].



(2R)-209

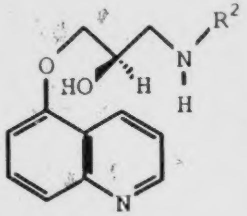
(2R)-214-215

214 $R^2 = -CH(CH_3)_2$, **215** $R^2 = -C(CH_3)_3$.

Scheme 16. The synthesis of (2R)-1-(quinol-5-yloxy)-3-isopropyl(or t-butyl)amino-2-propanols.

The physical data for (**214-215**).2HCl are presented in Table 14, and the ^1H nmr spectra and ir spectroscopic data are summarized in Table 15.

Table 14. Physical data for (2R)-1-(quinol-5-yloxy) -3-isopropyl(or t-butyl)amino-2-propanols.

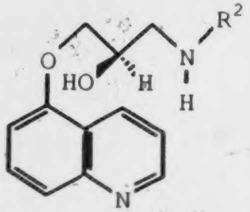


(2R)-**214**, (2R)-**215**

[a]Compd.	R^2	Reaction Time (h)	Yield,%	MP,°C	Formula	Microanalyses: Found (Calcd.) %C	%H	%N
214	$CH(CH_3)_2$	24	96	225	$C_{15}H_{22}N_2O_2Cl_2$	54.13	6.84	7.97
						(54.06)	(6.65)	(8.40)
215	$C(CH_3)_3$	36	95	222	$C_{16}H_{24}N_2O_2Cl_2$	55.22	7.10	7.96
						(55.34)	(6.97)	(8.07)

[a] The dihydrochloride salts of (**214-215**) were prepared since the free bases were oils which did not give acceptable microanalytical data.

Table 15. Ir^a and ^{1}H nmr^b spectral data for (2R)-1-(quinol-5-yloxy)-3-alkylamino-2-propanols (**214-215**).



(2R)-**214**, R^2= CH(CH$_3$)$_2$; (2R)-**215**, R$_2$= C(CH$_3$)$_3$.

^{c}Compd.	ir (cm^{-1})(OH)	^{1}H nmr δ (ppm)
214	3284	1.30 and 1.34 (two d, J= 6.54 Hz, 3H each, -NH-CH($\underline{CH_3}$)$_2$; 3.15 and 3.29 (two m, 2H total, -CH(OH)-$\underline{CH_2}$-NH-); 3.40 (m, 1H, -NH-$\underline{CH}$(CH$_3$)$_2$); 4.33 (m, 2H, -O-$\underline{CH_2}$-CH(OH)-]; 4.50 (m, 1H, -CH$_2$-$\underline{CH}$(OH)-CH$_2$-NH-); 4.8-5.4 (br s, 1H, OH, exchanges with deuterium oxide); 7.40 (d, J$_{6,7}$= 8.26 Hz, 1H, quinolyl H-6); 7.91 (d, J$_{7,8}$= 8.26 Hz, 1H, quinolyl H-8); 8.0 (m, 1H, quinolyl H-3); 8.04 (d, J$_{6,7}$= 8.26 Hz of d, J$_{7,8}$= 8.26 Hz, 1H, quinolyl H-7); 8.76 (br s, 1H, NH exchanges with deuterium oxide); 9.30 (d, J$_{2,3}$= 4.72 Hz, 1H, quinolyl H-2); 9.37 (br s, 1H, NH exchanges with deuterium oxide); 9.43 (d, J$_{3,4}$ = 8.26 Hz, 1H, quinolyl H-4).

Table 15. (cont.)

215	3279	1.35 (s, 9H, -NH-C($\underline{CH}_3$)$_3$; 3.08 and 3.27 (two m, 1H each, -CH(OH)-$\underline{CH}_2$-NH-); 3.9 (br s, 2H, -O$\underline{H}$ and -N$\underline{H}$, exchange with deuterium oxide); 4.28 [d, J_{vic}= 5.68 Hz of d, J_{gem}= 10.41 Hz, 1H, -O-C$\underline{H}$H^1-CH(OH)-]; 4.36[d, J_{vic}= 4.73 Hz of d, J_{gem}= 10.41 Hz, 1H, -O-CH$\underline{H}^1$-CH(OH)-]; 4.44 (m, 1H, -CH$_2$-$\underline{CH}$(OH)-CH$_2$-NH-); 7.34 (d, $J_{6,7}$= 8.4 Hz, 1H, quinolyl H-6); 7.9 (d, $J_{7,8}$= 8.4 Hz, 1H, quinolyl H-8); 7.94 (m, 1H, quinolyl H-3); 8.0 (d, $J_{6,7}$= 8.40 Hz of d, $J_{7,8}$= 8.4 Hz, 1H, quinolyl H-7); 8.69 (br s, 1H, N$\underline{H}$, exchanges with deuterium oxide); 9.24 (m, 2H, quinolyl H-2, H-4).

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[a] KBr.

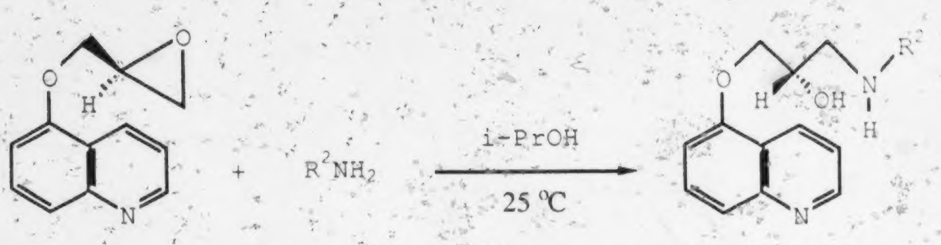
[b] The spectrum was determined in DMSO-d_6.

[c] Dihydrochoride salts.

The ^{1}H nmr spectra for compounds (**214-215**).2HCl indicated that the oxygen methylene protons (O-CH$_2$-) exhibited the same chemical shift, whereas the methylene protons attached to the isopropylamino and t-butylamino groups were chemically and magnetically non-equivalent. The ir spectra for compounds (**214-215**).2HCl exhibited absorptions in the 1638-1641 (C=N), 1280-1283 (aromatic-C-O), 1205 (aliphatic-C-O), 1107-1108 (alcohol C-O stretching vibrations), 2600-3284 (quaternary NH) and 3400 (OH) cm^{-1} ranges.

3.4.1.4.0 SYNTHESIS OF (2S)-1-(QUINOL-5-YLOXY)-3-ALKYLAMINO-2-PROPANOLS.

It is known that β-adrenergic blocking activity resides primarily in the levorotatory enantiomer which has the (S)-configuration[355,357,348]. Since many potent β-adrenergic blocking agents such as propranolol and practolol[356] possess the (S)-configuration, a series of (S)-1-(quinol-5-yloxy)-3-alkylamino-2-propanols were prepared to determine the effect of the (S)-configuration upon β-adrenergic antagonist activity. Reaction of (+)-(S)-1-(quinol-5-yloxy)-2,3-epoxypropane **(210)** with isopropylamine, t-butylamine or cyclohexylamine in 2-propanol at 25 °C for 24-36 h afforded (**216-217**) as oils and (**218**) as a white solid. The free bases (**216-217**) were converted to the corresponding dihydrochloride salts by reaction with anhydrous HCl in dry ether and subsequently recrystallized from absolute ethyl alcohol (92-98% yield) as outlined in Scheme 17. The physical data for (**216-218**) are presented in Table 16a, and the ^{1}H nmr and ir spectroscopic data are summarized in Table 17.

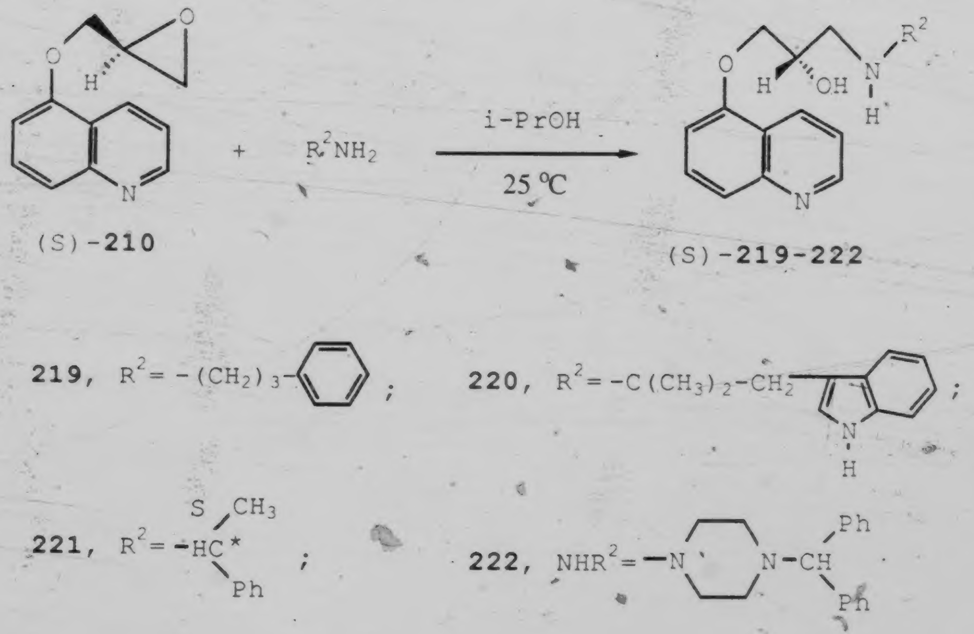


(2S)-210 **(2S)-216-222**

216, R^2= $-CH(CH_3)_2$; **217**, R^2= $-C(CH_3)_3$;
218, R^2= cyclohexyl.

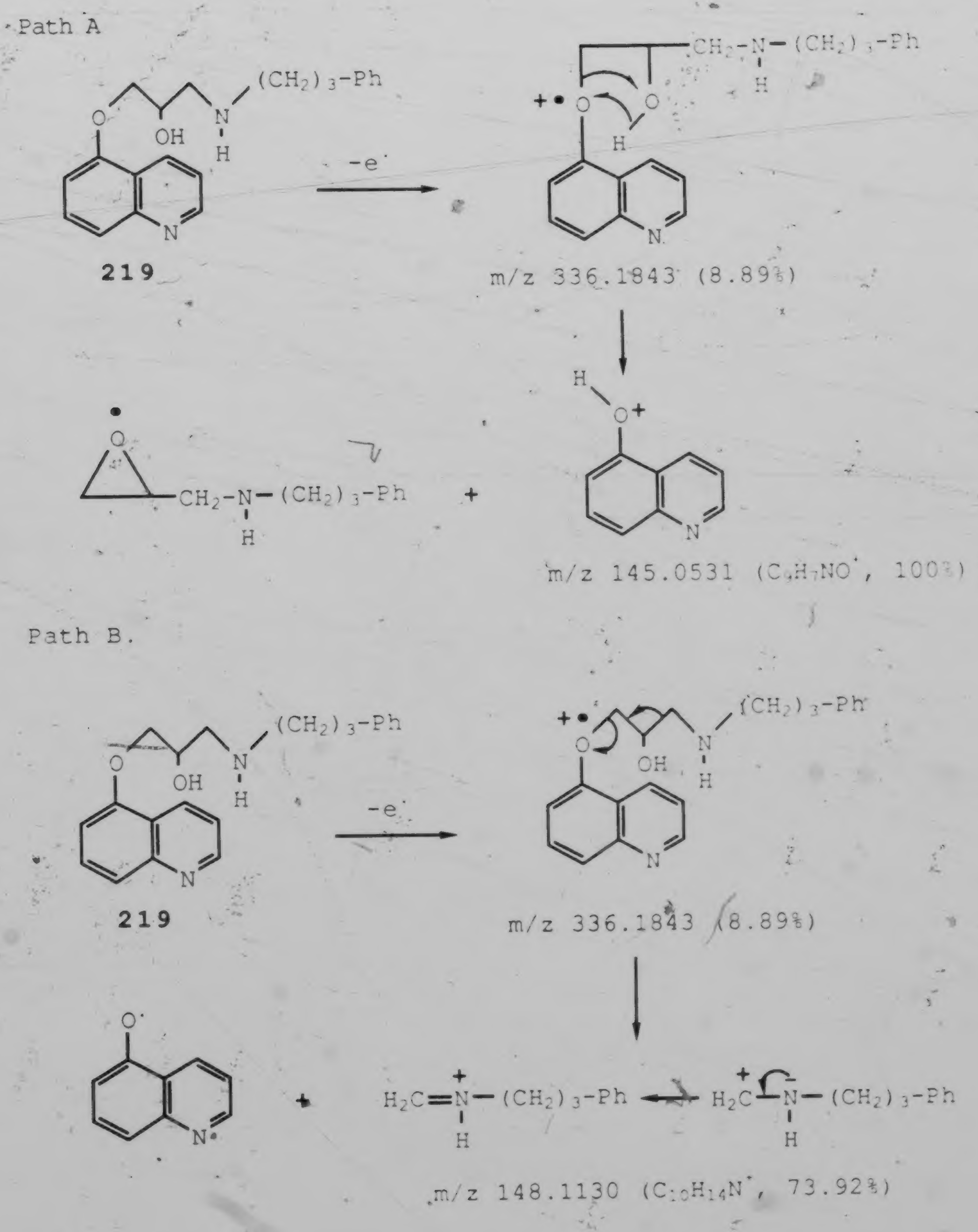
Scheme 17. The synthesis of (2S)-1-(quinol-5-yloxy)-3-isopropyl, (t-butyl or cyclohexyl)amino-2-propanols.

The ^1H nmr spectra for compounds (**216**).2HCl and the free base (**218**) indicated that the oxymethylene protons ($O-CH_2-$) exhibited the same chemical shift whereas, the corresponding $-OCH_2-$ protons for (**217**).2HCl were chemically and magnetically non-equivalent. The methylene protons attached to the isopropylamino (**216**).2HCl and t-butylamino (**217**).2HCl were chemically non-equivalent whereas the corresponding methylene protons attached to the cyclohexylamino (**218**) were chemically and magnetically non-equivalent. The optical rotation for (**216**).2HCl was $[\alpha]_D^{23}$ = -10.84° (c = 0.03, MeOH). Further modifications to compound (**216**) were made where the R^2 isopropyl substituent was replaced by an arylalkyl substituent such as 1-(3-phenylpropyl) (**219**), 3-indolyl-t-butyl substituent (**220**), a second (S)-α-methylbenzyl (**221**), or replacement of the isopropylamino moiety by a tertiary amino group such as a N^4-diphenylmethylpiperazinyl group that provided (**222**). These compounds are listed in Scheme 18.


(S)-**210**
+
R^2NH_2
i-PrOH
25 °C
(S)-**219-222**
219, $R^2 = -(CH_2)_3-$;
220, $R^2 = -C(CH_3)_2-CH_2$;
221, $R^2 = -HC^*$ S CH3 Ph ;
222, $NHR^2 = $ N N-CH Ph Ph

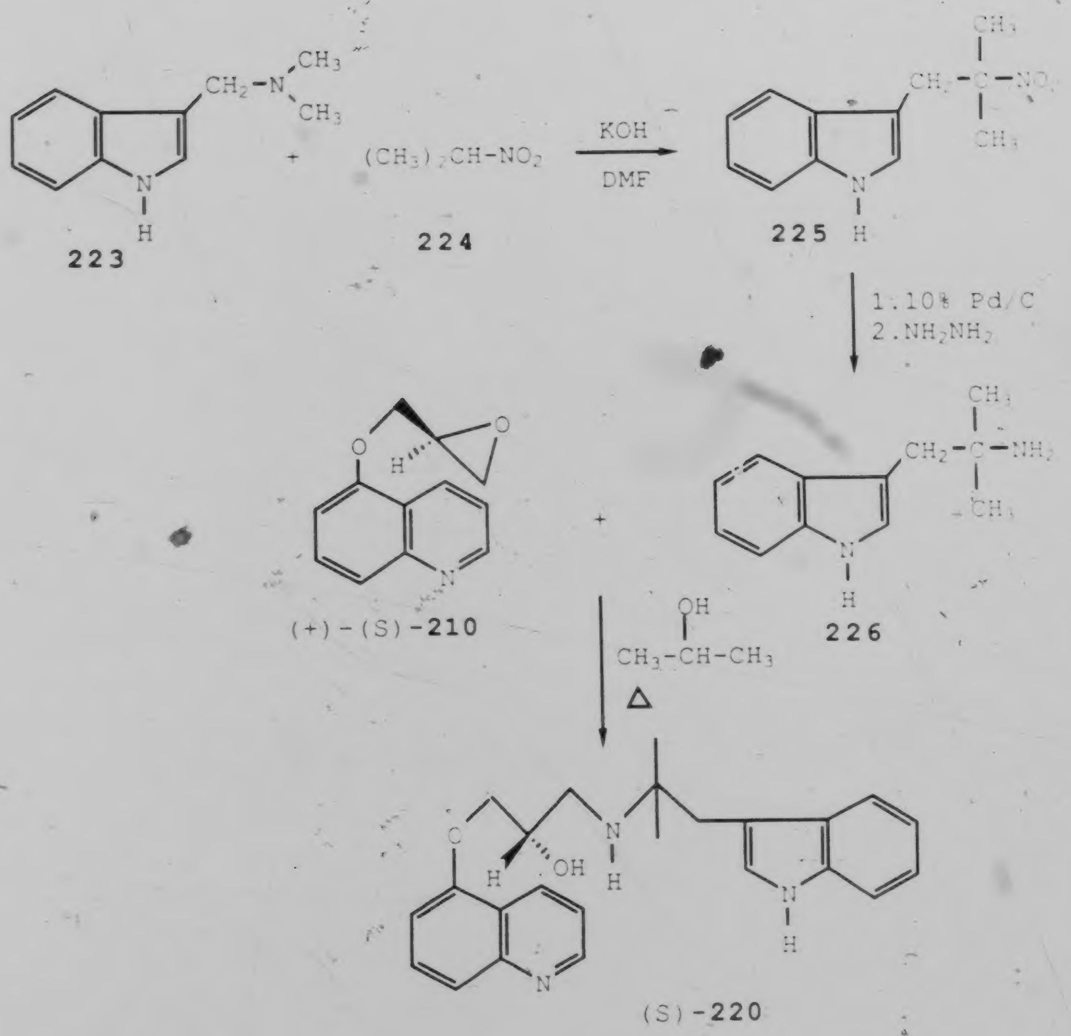
Scheme 18. The synthesis of (2S)-1-(quinol-5-yloxy)-3-[phenyl-1-propyl, (S)-α-methylbenzyl, or 2-(3-indolyl)-1,1-dimethylethyl]amino or 1-(4-diphenylmethylpiperazinyl]-2-propanols

A mixture of (+)-(S)-(**210**) and 1 equivalent of 3-phenyl-1-propylamine in 2-propanol was heated at reflux for 5 h to yield (**219**) after purification on silica gel G plates using ether:methanol (7:3 v/v) as the development solvent. Extraction of the band having R_f 0.48 with methanol gave (**219**) as a colorless liquid in 90% yield. The physical data for (S)-(**219**) are presented in Table 16b. The structure assigned to (2S)-1-(quinol-5-yloxy)-3-(3-phenyl-1-propylamino)-2-propanol (**219**) was consistent with the ir and ^1H nmr data shown in Table 17. The high resolution mass spectrum exhibited a molecular ion at m/z 336.1843. Fragmentaion of the molecular ion occurrs via the two major pathways illustrated in Scheme 19.

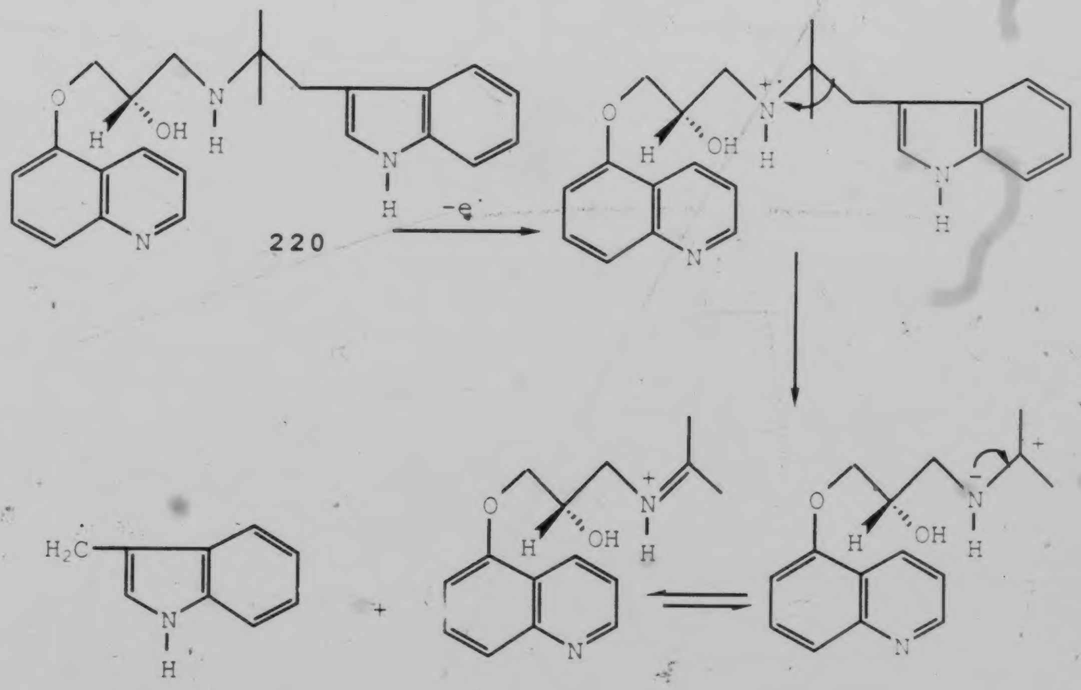

Path A
(CH2)3-Ph
O
OH
N
H
N
219
-e·
+•
O
O
H
CH2-N-(CH2)3-Ph
H
N
m/z 336.1843 (8.89%)
H
O+
N
m/z 145.0531 (C9H7NO+, 100%)
•
O
CH2-N-(CH2)3-Ph
H
+
Path B.
(CH2)3-Ph
O
OH
N
H
N
219
-e·
+•
O
OH
N
H
(CH2)3-Ph
N
m/z 336.1843 (8.89%)
O·
N•
+
H2C=N+-(CH2)3-Ph
H
H2C+-N-(CH2)3-Ph
H
m/z 148.1130 (C10H14N+, 73.92%)

Scheme 19. Major fragmentations of (2S)-1-(quinol-5-yloxy)-3-(3-phenyl-1-propyl)amino-2-propanol (**219**).

Replacement of an alkyl nitrogen substituent present in class B aryloxypropanolamine by a 1,1-dimethyl-2-(1H-indol-3-yl)ethyl group, referred to as 3-indolyl-t-butyl, that possessed both antihypertensive and vasodilating activities has been reported[344,446]. It was therefore of interest to replace the isopropyl group present in (**216**) by a 3-indolyl-t-butyl substituent to determine the effect which this replacement has upon β-adrenergic antagonist activity. A mixture of (+)-(S)-(**210**) and 3-indolyl-t-butylamine (**226**), which was prepared by a literature procedure[344,446] with some modifications, in a small amount of 2-propanol was heated at reflux for 12 h, as outlined in Scheme 21. Compound (**220**) was obtained as a white solid in 80% yield after purification by recrystallization from ether:hexane or preparative tlc chromatography using chloroform:ethanol (7:3 v/v) as development solvent and extraction of the band at R_f= 0.48. The physical data for (S)-(**220**) are presented in Table 16b. The structure assigned to (**220**) was consistent with its ir and ^{1}H nmr spectral data that are listed in Table 17. The ir spectrum indicated the presence of an indole NH at 3411, a CH at 3286, a C=N at 1617, an aromatic C-O at 1267, an aliphatic C-O at 1172 and an alcohol C-O at 1096 cm^{-1}. The high resolution mass spectrum displayed a molecular ion at m/z 389.2089 ($C_{24}H_{27}N_3O_2$). The major fragmentation was expulsion of a 3-methylindole radical from the molecular ion to give the base peak at m/z 259.1451 (($C_{15}H_{19}N_2O_2{}^+$) as shown in Scheme 21.


CH2-N
CH3
CH3
N
H
223
+
(CH3)2CH-NO2
224
KOH
DMF
CH3
CH2-C-NO2
CH3
N
H
225
1. 10% Pd/C
2. NH2NH2
CH3
CH2-C-NH2
CH3
N
H
226
O
H
O
N
(+)-(S)-210
+
OH
CH3-CH-CH3
Δ
O
H
OH
N
H
N
N
H
(S)-220

Scheme 20. Synthesis of (2S)-1-(quinol-5-yloxy)-3-[2-(3-indolyl)-1,1-dimethylethyl]amino-2-propanol (**220**).



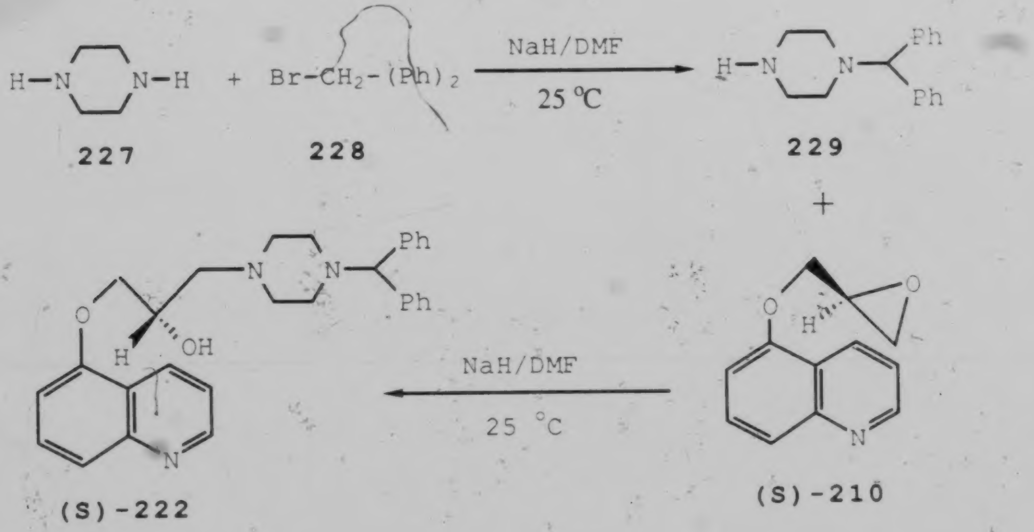
m/z 259.1451 ($C_{15}H_{19}N_2O_2^{+}$, 100%)

Scheme 21. Major fragmentation of (2S)-1-(quinol-5-yloxy)-3-[2-(3-indolyl)-1,1-dimethylethyl]amino-2-propanol (**220**).

Incorporation of a second chiral carbon onto the side chain amino group of class A arylethanolamines, enhanced β-adrenergic agonist activity and receptor affinity[161,162]. It was therefore of interest to replace the isopropyl substituent of (S)-(**216**) by a (S)-α-methylbenzyl substituent such that the effect upon β-adrenergic activity could be determined. The target compound (**221**) was prepared by reaction of (+)-(S)-(**210**) and one equivalent of (S)-α-methyl-benzylamine in 2-propanol at 25 °C for 36 h. The vicous oil obtained which was recrystallized from ether:hexane to afford (SS)-(**221**) as a white solid in

95% yield. The physical data for (**221**) are presented in Table 16b, and the ^{1}H nmr and ir spectroscopic data are summarized in Table 17.

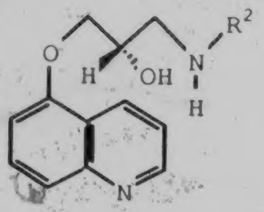
The replacement of an alkylamino moiety of class B aryloxypropanolamines by a N^4-arylpiperazinyl group has provided a large number of active compounds[330]. These results stimulated us to investigate the synthesis of (**222**) as outlined in Scheme 22.



Scheme 22. Synthesis of (2S)-1-(quinol-5-yloxy)-3-[1-(4-diphenylmethyl-piperazinyl]-2-propanol (**222**).

Reaction of 1-(diphenylmethyl)piperazine (**229**) prepared from piperazine and benzhydryl bromide (**228**) with (+)-(S)-(**210**) in 2-propanol aforded a liquid which was recrystallized from ether:hexane to give (S)- (**222**) as a white solid in 93% yield. The physical data for (S)-(**222**) are presented in Table 16b, and the ^{1}H nmr and ir spectroscopic data are summarized in Table 17. The ir spectrum showed the presence of a free OH at 3400, C=N at 1617, aromatic C-O at 1267, aliphatic C-O at 1201 and alcohol C-O 1095-1141 cm^{-1}.

Table 16a. Physical data for (2S)-1-(quinol-5-yloxy) -3-isopropyl(t-butyl or cyclohexyl)amino-2-propanols.



(2S)-**216-218**

Compd.	R^2	Reaction Time (h)	Yield,%	MP,°C	Formula	Microanalyses: Found (Calcd.) %C	%H	%N
216[a,b]	$CH(CH_3)_2$	24	98	229	$C_{15}H_{22}N_2O_2Cl_2$	53.68	6.82	8.04
						(54.06)	(6.65)	(8.40)
217[a]	$C(CH_3)_3$	36	98	214	$C_{16}H_{24}N_2O_2Cl_2$	54.95	6.96	7.72
						(55.34)	(6.97)	(8.07)
218[c]	Cyclohexyl	36	92	96	$C_{18}H_{24}N_2O_2$	72.05	7.96	9.31
						(71.97)	(8.05)	(9.33)

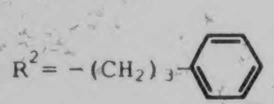
---

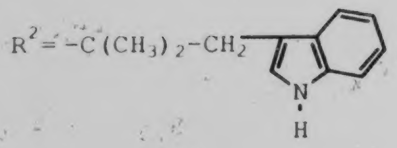
[a] The dihydrochloride salts of **(216-217)** were prepared since the free bases were oils which did not give acceptable microanalytical data.

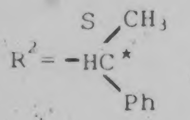
[b] Optical rotation was $[\alpha]_D^{23} = -10.84$ (c 0.03, MeOH).

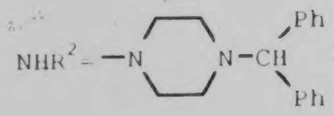
[c] Free base.

Table 16b. Physical data for (2S)-1-(quinol-5-yloxy)-3-arylalkylamino-2-propanols.

219,

;

220,

;

221,

$R^2 = -HC^{*}(SCH_3)(Ph)$;

222,


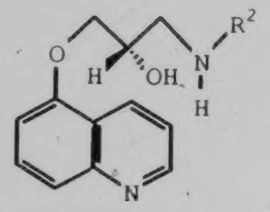
[a]Compd.	Reaction Time (h)	Yield,%	MP,°C	Formula	Exact mass Calcd.	Exact mass Found	Microanalyses: Found (Calcd.) %C	Microanalyses: Found (Calcd.) %H	Microanalyses: Found (Calcd.) %N
219	40	90	oil	$C_{21}H_{24}N_2O_2$	336.1838	336.1843			
220	12[b]	80	80	$C_{24}H_{27}N_3O_2$	389.2103	389.2091			
221	36	95	59	$C_{20}H_{22}N_2O_2$			74.79 (74.50)	6.74 (6.87)	8.78 (8.68)
222	3[c]	93	139	$C_{29}H_{31}N_3O_2$	453.2416	453.2417			

[a] Free base.

[b] Heating at reflux .

[c] Heating at reflux for 3 hr and stirring at room temperature for a further 12 hr.

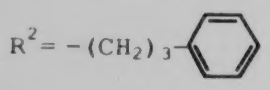
Table 17. Ir[a,b] and ^{1}H nmr[c,d] spectral data for (2S)- 1-(quinol-5-yloxy)-3-alkyl(arylalkyl)amino-2-propanols (**216-222**).



(2S)-**216-222**

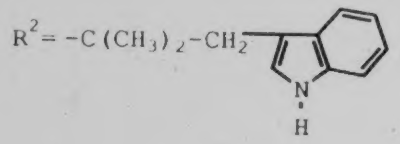
216, R^2= $-CH(CH_3)_2$; **217**, R^2= $-C(CH_3)_3$; **218**, R^2= Cyclohexyl;

219,



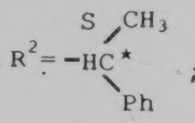
;

220,



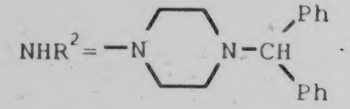
;

221,



;

222,



Compd.	ir (cm^{-1})(OH)	^{1}H nmr δ (ppm)
216[c,e]	3320[b]	1.29 and 1.32 (two d, J= 5.5 Hz, 3H each, -NH-CH(CH$_3$)$_2$; 3.14 and 3.27 (two m, 1H each, -CH(OH)-CH$_2$-NH-); 3.40 (m, 1H, -NH-CH(CH$_3$)$_2$); 4.31 [m, 2H, -O-CH$_2$-

Table 17. (cont.)

		CH(OH)-]; 4.48 (m, 1H, -CH$_2$-$\underline{\text{CH}}$(OH)-CH$_2$); 4.9-5.3 (br s, 2H, O$\underline{\text{H}}$, exchanges with deuterium oxide); 7.37 (d, $J_{6,7}$= 8.4 Hz, 1H, quinolyl H-6); 8.0 (m, 3H, quinolyl H-3, H-7, H- 8); 8.82 (br s, 1H, N$\underline{\text{H}}$, exchanges with deuterium oxide); 9.28 (d, $J_{2,3}$= 5.55 Hz of d, $J_{2,4}$= 1.65 Hz, 1H, quinolyl H-2); 9.31 (br s, 1H, N$\underline{\text{H}}$, exchanges with deuterium oxide); 9.37 (d, $J_{3,4}$= 7.7 Hz of d, $J_{2,4}$= 1.65 Hz, 1H, quinolyl H-4).
217^c	3385^b	1.36 (s, 9H, -NH-C($\underline{\text{CH}}_3$)$_3$; 3.06 and 3.26 (two m, 1H each, -CH(OH)-$\underline{\text{CH}_2}$-NH-); 3.3 [d, J_{vic}= 5.5 Hz of d, J_{gem}= 8.8 Hz, 1H, -O-C$\underline{\text{H}}$H^1-CH(OH)-]; 3.38 [d, J_{vic}= 4.4 Hz of d, J_{gem}= 8.8 Hz, 1H, -O-CH$\underline{\text{H}}^1$-CH(OH)-]; 3.48 (m, 1H, -CH$_2$-$\underline{\text{CH}}$(OH)-CH$_2$-NH-); 3.5 (br s, 1H, OH, exchanges with deuterium oxide); 7.39 (d, $J_{6,7}$= 8.19 Hz, 1H, quinolyl H-6); 8.0 (m, 3H, quinolyl H-3, H-7, H- 8); 8.74 (br s, 1H, NH exchanges with deuterium oxide); 9.31 (d, $J_{2,3}$= 5.04 Hz of d, $J_{2,4}$= 1.89 Hz, 1H, quinolyl H-2); 9.36 (br s, 1H, NH exchanges with deuterium oxide); 9.42 (d, $J_{3,4}$= 8.82 Hz of d, $J_{2,4}$= 1.89 Hz, 1H, quinolyl H-4).
218^d	3192^b	1.04-2.02(m, 10H, cyclohexyl hydrogens); 2.51 [m, 1H, (cyclohexyl C-1H)]; 2.87 (d, J_{vic}= 6.93 Hz of d, J_{gem}= 11.88 Hz, 1H, -CH(OH)-C$\underline{\text{H}}$H^1-NH-); 3.06 (d, J_{vic}= 3.96

Table 17. (cont.)

		Hz of d, J_{gem}= 11.88 Hz, 1H, -CH(OH)-CH$\underline{\mathrm{H}}^{1}$-NH-)]; 3.1 (br s, 2H, O$\underline{\mathrm{H}}$ and N$\underline{\mathrm{H}}$, exchange with deuterium oxide); 4.18 [m, 3H; O-$\underline{\mathrm{CH}_2}$-CH(OH)-, -CH$_2$-$\underline{\mathrm{CH}}$(OH)-CH$_2$); 6.86 (d, $J_{6,7}$= 7.7 Hz, 1H, quinolyl H-6); 7.37 (d, $J_{3,4}$= 8.47 Hz of d, $J_{2,3}$= 4.62 Hz, 1H, quinolyl H-3); 7.6 (d, $J_{6,7}$= 7.7 Hz of d, $J_{7,8}$= 7.7 Hz, 1H, quinolyl H-7); 7.72 (d, $J_{7,8}$= 7.7 Hz,1H, quinolyl H-8); 8.58 (d, $J_{3,4}$= 8.47 Hz of d, $J_{2,4}$= 1.54 Hz, 1H, quinolyl H-4); 8.9 (d, $J_{2,3}$= 4.62 Hz of d, $J_{2,4}$= 1.54 Hz, 1H, quinolyl H-2).
219^{d}	3273^{a}	1.86 (quintet, J= 8Hz, 2H, -NH-CH$_2$-$\underline{\mathrm{CH}_2}$-CH$_2$-Ph); 2.72 (m, 4H, -NH-$\underline{\mathrm{CH}_2}$-CH$_2$-$\underline{\mathrm{CH}_2}$-Ph); 2.85 and 2.98 (two m, 1H each, -CH(OH)-$\underline{\mathrm{CH}_2}$-NH-); 4.18 (m, 3H, -O-$\underline{\mathrm{CH}_2}$-CH(OH)-, -CH$_2$-$\underline{\mathrm{CH}}$(OH)-CH$_2$-); 6.88 (d, $J_{6,7}$= 8.25 Hz, 1H, quinolyl H-6); 7.20-7.32 (m, 5H, phenyl hydrogens); 7.37 (d, $J_{3,4}$= 8.25 Hz of d, $J_{2,3}$= 4.50 Hz, 1H, quinolyl H-3); 7.61 (d, $J_{6,7}$= 8.25 Hz of d, $J_{7,8}$= 8.25 Hz, 1H, quinolyl H-7); 7.72 (d, $J_{7,8}$= 8.25 Hz, 1H, quinolyl H-8); 8.57 (d, $J_{3,4}$= 8.25 Hz of d, $J_{2,4}$= 1.50 Hz, 1H, quinolyl H-4); 8.91 (d, $J_{2,3}$= 4.50 Hz of d, $J_{2,4}$= 1.50 Hz, 1H, quinolyl H-2).
220^{d}	3411^{b}	1.18 and 1.19 (2 s, 3H each, -CH$_2$C($\underline{\mathrm{CH}_3}$)$_2$NH-); 2.92 (d, J_{vic}= 7.00 Hz of d, J_{gem}= 12.0 Hz, 1H, -CH(OH)-C$\underline{\mathrm{H}}$H^{1}-NH-); 2.90 [s, 2H, -NH-C(CH$_3$)$_2$$\underline{\mathrm{CH}_2}$-indol]; 3.03 (d,

Table 17. (cont.)

		J_{vic}= 4.0 Hz of d, J_{gem}= 12.0 Hz, 1H of -CH(OH)-CH$\underline{H}^1$-NH-)]; 3.1 ((br s, 2H, O$\underline{H}$ and N$\underline{H}$, exchange with deuterium oxide); 4.14 [m, 3H; -O-$\underline{CH}_2$-, -CH_2-$\underline{CH}$(OH)-]; 6.83 (d, $J_{5,6}$= 8.2 Hz, quinolyl H-6); 7.04 (d, $J_{CH,NH}$= 1.5 Hz, 1H, indolyl H-2); 7.12 (d, $J_{5,6}$= 7.5 Hz of d, $J_{6,7}$= 7.5 Hz of d, $J_{4,6}$= 1.5 Hz, 1H, indolyl H-6); 7.18 (d, $J_{4,5}$= 7.5 Hz of d, $J_{5,6}$= 7.5Hz of d, $J_{5,7}$= 1.5 Hz, 1H, indolyl H-5); 7.28 (d, $J_{3,4}$= 8.25 Hz of d, $J_{2,3}$= 4.5 Hz, 1H, quinolyl H-3); 7.32 (d, $J_{4,5}$= 7.5 Hz of d, $J_{4,6}$= 1.5 Hz, 1H, indolyl H-4); 7.58 (d, $J_{6,7}$= 8.25 Hz of d, $J_{7,8}$= 8.25 Hz, 1H, quinolyl H-7); 7.64 (d, $J_{6,7}$= 7.5 Hz, 1H, indolyl H-7); 7.72 (d, $J_{7,8}$= 8.25 Hz, 1H, quinolyl H-8); 8.42 (br s, 1H, indolyl -N$\underline{H}$, exchanges with deuterium oxide); 8.5 (d, $J_{3,4}$= 8.25 Hz of d, $J_{2,4}$= 1.5 Hz, 1H, quinolyl H-4); 8.98 (d, $J_{2,3}$= 4.5 Hz of d, $J_{2,4}$= 1.5 Hz, 1H, quinolyl H-2).
221^d	3240^b	1.39 and 1.41 [two d, J= 6.0 Hz, 3 H total, -NH-CH($\underline{CH}_3$)(Ph)]; 2.43 (br s, 2H, -$\underline{OH}$ and -NH, exchange with deuterium oxide); 2.69 (d, J_{vic}= 7.50 Hz of d, J_{gem}= 12.75 Hz, 1H, -C$\underline{H}$H^1-NH-)]; 2.88 (d, J_{vic}= 4.50 Hz of d, J_{gem}= 12.75 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-)]; 3.86 [q, J= 6.0 Hz, 1H, -NH-$\underline{CH}$(CH_3)(Ph)]; 4.10 [m, 2H, -O-$\underline{CH}_2$-

Table 17. (cont.)

		CH(OH)-]; 4.20 [m, 1H, -CH_2-$\underline{CH}$(OH)-CH_2-]; 6.81 (d, $J_{6,7}$= 8.25 Hz, 1H, quinolyl H-6); 7.20-7.36 (m, 6H, quinolyl H-3, phenyl hydrogens); 7.57 (d, $J_{6,7}$= 8.25 Hz of d,$J_{7,8}$= 8.25 Hz, 1H, quinolyl H-7); 7.67 (d, $J_{7,8}$= 8.25 Hz, 1H, quinolyl H-8); 8.40 (d, $J_{3,4}$= 8.25 Hz of d, $J_{2,4}$= 1.5 Hz, 1H, quinolyl H-4); 8.87 (d, $J_{2,3}$= 4.5 Hz of d, $J_{2,4}$= 1.5 Hz, 1H, quinolyl H-2).
222[d]	3403[b]	1.61 (br s, 1H, -OH, exchange with deuterium oxide); 2.50 and 2.76 (two m, 4H each, piperazinyl hydrogens); 2.66 (m, 2H, -CH(OH)-$\underline{CH_2}$-NH-); 4.16 [m, 2H, -O-$\underline{CH_2}$-CH(OH)-]; 4.22 (m, 1H, -CH_2-$\underline{CH}$(OH)-CH_2-]; 4.26 (s, 1H, -piperazinyl-$\underline{CH}(Ph)_2$]; 6.88 (d, $J_{5,6}$= 8.25 Hz, 1H, quinolyl H-6); 7.2 (d, J= 7.5 Hz of d, J= 7.5 Hz, 2H, phenyl *para* hydrogens); 7.29 (t, , J= 7.5 Hz, 4H, phenyl *meta* -hydrogens); 7.38 (d, $J_{3,4}$= 8.25 Hz of d, $J_{2,3}$= 4.5 Hz, 1H, quinolyl H-3); 7.43 (d, J= 7.5 Hz, 4H, phenyl *ortho* -hydrogens); 7.60 (d, $J_{6,7}$= 8.25 Hz of d, $J_{7,8}$= 8.25 Hz, 1H, quinolyl H-7); 7.71 (d, $J_{7,8}$= 8.25 Hz, 1H, quinolyl H-8); 8.59 (d, $J_{3,4}$= 8.25 Hz of d, $J_{2,4}$= 1.5 Hz, 1H, quinolyl H-4); 8.92 (d, $J_{2,3}$= 4.50 Hz of d, $J_{2,4}$= 1.50 Hz, 1H, quinolyl H-2).

---

[a]Film , [b]KBr . The ^{1}H nmr spectrum was determined in [c]DMSO-d_6 for dihydrochloride salts and [d]$CDCl_3$ for free bases.
[e]Optical rotation was $[\alpha]_D^{23}$= -10.84 (c= 0.03, MeOH).

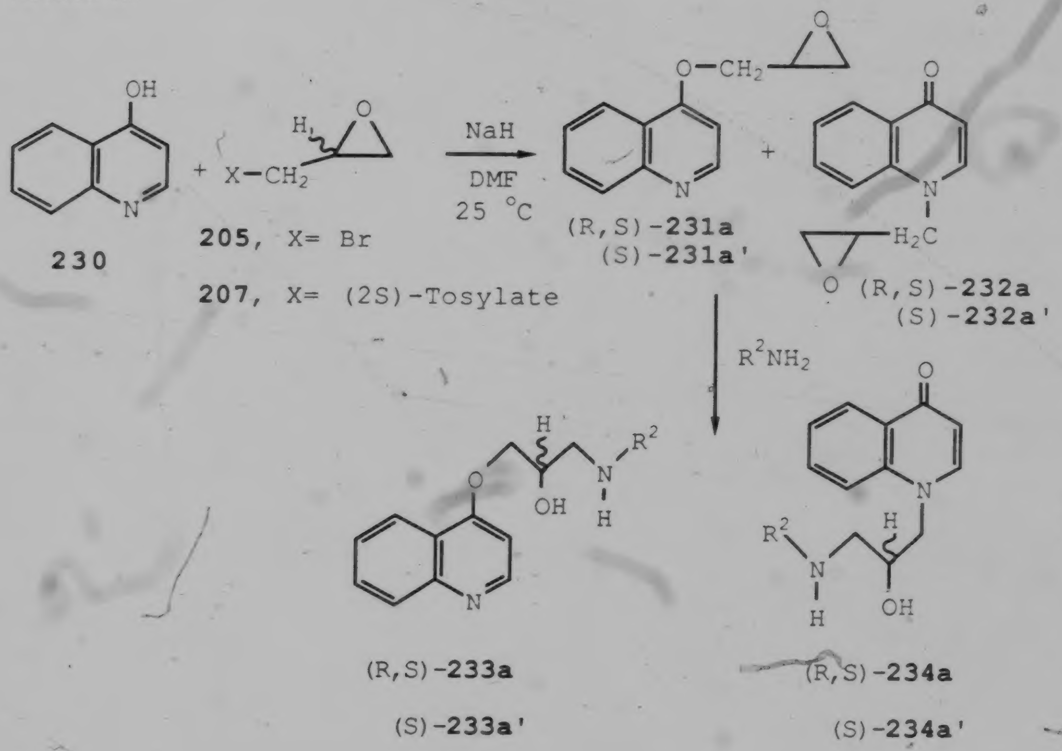
3.4.2.0.0 SYNTHESIS OF (R,S)-1-(QUINOL-4-YLOXY)-3-ISOPROPYLAMINO-2-PROPANOL AND (R,S)-1-(QUINOL-2-YLOXY)-3-ALKYLAMINO-2-PROPANOLS.

The series of compounds (**216-222**) described previously possessing a propanolamine group that is attached to the 5-position of quinoline exhibited a very potent and selective β_1/β_2 β-adrenergic receptor antagonist activity. These encouraging results prompted further studies to determine the structure-activity correlations for the isomeric 2- and 4-quinolyl analogues.

3.4.2.1.0 SYNTHESIS OF (R,S)-1-(QUINOL-4-YLOXY)-2,3-EPOXYPROPANE, AND (R,S)-1-[1-(1,4-DIHYDROQUINOLIN-4-ONE)]-2,3-EPOXYPROPANE.

The reaction of 4-hydroxyquinoline (**230**) with epibromohydrin in the presence of NaH and DMF at 25 ^{o}C afforded both O-alkylated (**231a**) and N-alkylated (**232a**) products which were separated by fractional crystallization from ether:hexane to afford pure (**232a**) in 68% yield as a yellow solid with a mp of 106 ^{o}C. The residue from the mother liquor was purified by preparative tlc chromatography using ether:ethanol (9:1 v/v) as development solvent. Extraction of the band having R_f= 0.40 with methanol gave (**231a**) as an oil in 10% yield. Extraction of the band having R_f= 0.10 afforded additional (**232a**) in 3% yield as outlined in Scheme 23, method A. The ratio of N:O alkylated products was about 7:1. The structures assigned to (**231a** and **232a**) were consistent with their ir and ^{1}H nmr spectra as presented in Table 18.

Method A.


OH
N
230
+ X—CH$_2$
H
O
205, X= Br
207, X= (2S)-Tosylate
NaH
DMF
25 °C
O—CH$_2$
(R,S)-231a
(S)-231a'
+
O
N
H$_2$C
(R,S)-232a
(S)-232a'
R^{2}NH$_2$
H
R^2
N
H
OH
(R,S)-233a
(S)-233a'
(R,S)-234a
(S)-234a'

Scheme 23. Synthesis of (2R,2S)-, and (2S)-1-[quinol-4-yloxy]-3-isopropylamino-2-propanols (**233a**) and (**233a'**); and (2R,2S)- and (2S)-1-[1-(1,4-dihydroquinolin-4-one)]-3-isopropylamino-2-propanol (**234a**) and (**234a'**).

The ir spectrum (cm^{-1}) for (**231a**) showed the presence of C=N (1621), aromatic C-O (1276) and epoxide C-O (1250) absorptions, whereas (**232a**) displayed absorptions for C=C at 1610 and C=O at 1633 cm^{-1}. The low frequency for the C=O absorption for (**232a**) is attributed to conjugation with the α,β-olefinic group and the aryl ring. The ^{1}H nmr for the O-alkylation product (**231a**) and N-alkylation product (**232a**) were sufficiently different to allow facile structure assignments. For example the heteroaryl C-2H of (**231a**) is at lower field (δ 8.81) than the C-2H of (R,S)-(**232a**) which appeared at δ 7.58. Furthermore, the $J_{2,3}$ coupling constant of 7.7 Hz for (R,S)-(**232a**) is much larger than the $J_{2,3}$ coupling constant of 5.0 Hz for (**231a**).

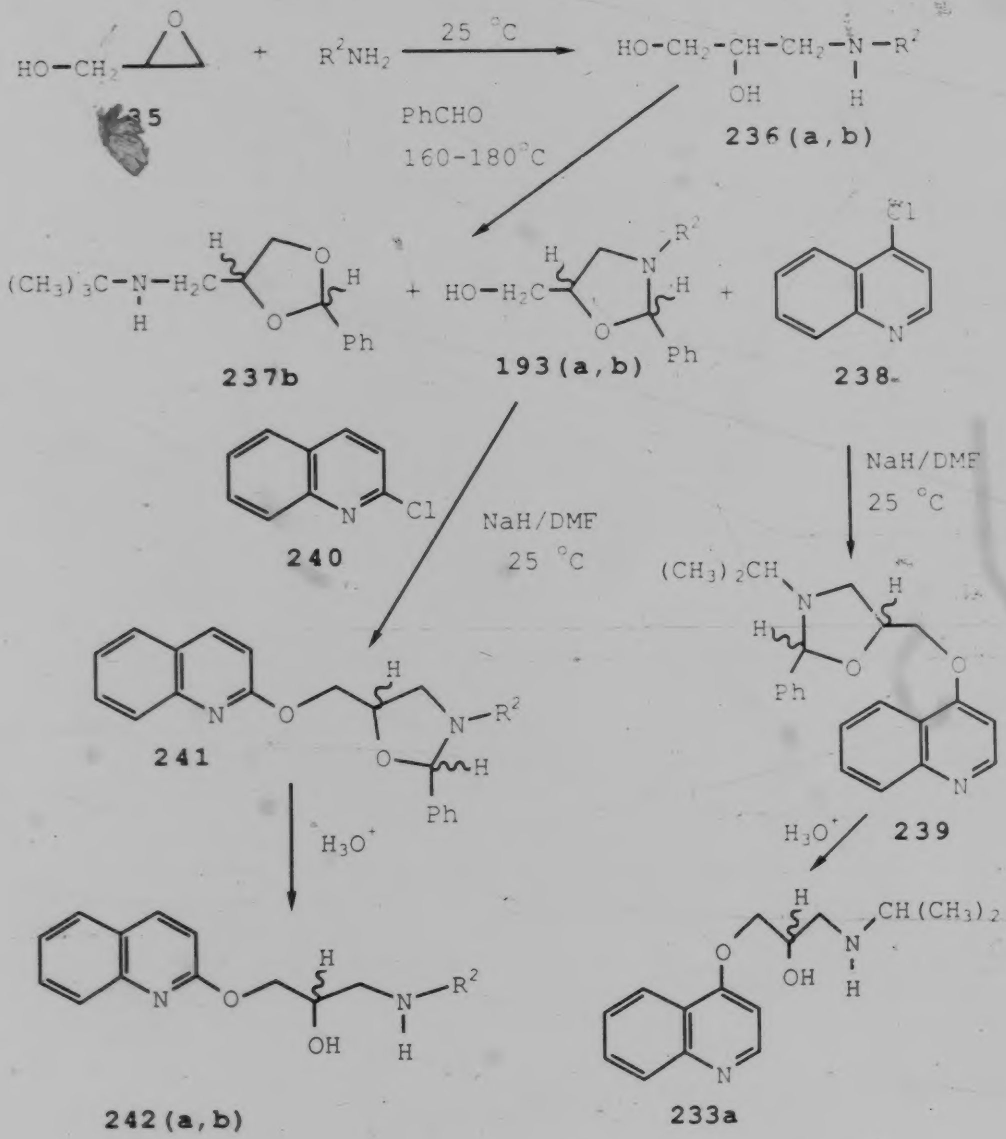
3.4.2.2.0 SYNTHESIS OF (S)-1-(QUINOL-4-YLOXY)-2,3-EPOXYPROPANE, (S)-1-[1-(1,4-DIHYDROQUINOLIN-4-ONE)]-2,3-EPOXYPROPANE.

(S)-1-(quinol-4-yloxy)-2,3-propane (**231a'**) was prepared as described for (**231a**) in section 3.4.2.1.0. A mixture of (S)-O-alkylated (**231a'**) and (S)-N-alkylated products (**232a'**) were separated by preparative tlc chromatography using ether:ethanol (9:1 v/v) as development solvent. Extraction of the band having R_f 0.48 with methanol gave (S)-(**231a'**) as an oil in 8% yield. Extraction of the band having R_f 0.10 with methanol gave the (S)-N-alkylated product (**232a'**) as an oil in 80% yield which was used without characterization by ^{1}H nmr spectrometry. The structure assigned to (S)-(**231a'**) was consistent with its ir and ^{1}H nmr spectra as presented in Table 18. The enantiomeric purity of (S)-(**231a'**) was determined by acquisition of ^{1}H nmr (δ) spectra in the presence of a chiral shift reagent (CSR). Similar information to that illustrated in Table 11 indicates that the ^{1}H triplet at (δ) 2.91 assigned to H_A collapsed to a singlet at a CSR concentration of 2 x 10^{-5} M and it is shifted to lower field.

3.4.2.3.0 SYNTHESIS OF (R,S),(S)-1-(QUINOL-4-YLOXY)-3-ISOPROPYLAMINO-2-PROPANOLS, AND (R,S)-,(S)-1-[1-(1,4-DIHYDROQUINOLIN-4-ONE)]-3-ISOPROPYLAMINO-2-PROPANOLS.

The subsequent reaction of (R,S)-(**231a** and **232a**) or (S)-(**231a'** and **232a'**) with isopropylamine in 2-propanol at 25 °C for 24 h afforded the respective free bases (R,S)-(**233a** and **234a**) as solids or (S)-(**233a'** and **234a'**) as oils with the retained configuration[452] as illustrated in Scheme 23. Dissolution of the free bases (**233a'** or **234a**) in dry ether, treatment with anhydrous HCl gas until no further precipitation of (**233a' or 234a**) was observed, followed by recrystallization from absolute ethanol yielded (**233a' or 234a**) respectively as the 2HCl salts in 92% yield. The physical data for (**233a**, **233a'**.2 HCl, and **234a**) are presented in Table 20. The structures assigned to (**233a**, **233a'**.2 HCl, **234a** and **234a'**) were consistent with their ir and ^{1}H nmr spectra as presented in Table 21. The low yield of the target O-alkylation intermediate (**231a**), prompted us to use an alternative method to synthesize 1-(quinol-4-yloxy)-3-alkylamino-2-propanols (**233a**) as outlined by method B in Scheme 24. A mixture of glycidol (**235**) and excess of isopropyl- or t-buylamine was allowed to react at 25 °C for 24 h to give the respective 3-(isopropylamino)-1,2-propandiol (**236a**) in 97% yield or 3-(t-butylamino)-1,2-propandiol (**236b**) in 98% yield. The structures assigned to (**236a** and **236b**) were consistent with their ir and ^{1}H nmr (see in Table 19). Examination of the ^{1}H nmr spectra for (**236a** and **236b**) indicated that the oxymethylene protons [HO-C$\underline{H}_2$-CH(OH)-] and aminomethylene protons (-CH_2-NHR^2) were chemically and magnetically non-equivalent. The ir spectra of **236(a,b)** showed a hydroxyl absorption at 3254 cm^{-1}. The subsequent reaction of **236a** with excess benzaldehyde at 160-180 °C for 5 h afforded **193a** [R^2= $CH(CH_3)_2$] in 80% yield.

Method B.

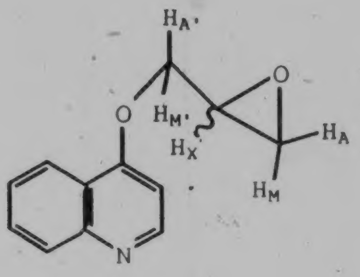

235
25 °C
236(a,b)
PhCHO
160-180°C
237b
193(a,b)
238
240
NaH/DMF
25 °C
NaH/DMF
25 °C
241
239
H_3O^+
H_3O^+
242(a,b)
233a

a, R^2= $CH(CH_3)_2$; **b**, R^2= $C(CH_3)_3$.

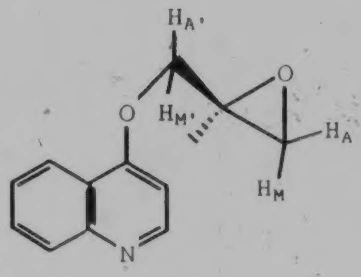
Scheme 24. Synthesis of 1-(quinol-2-yloxy)-3-alkylamino-2-propanols (**242**) and 1-(quinol-4-yloxy)-3-isopropylamino-2-propanol (**233a**).

In contrast, a similar reaction using **236b** with benzaldehyde afforded a mixture of **193b** and **237b** [R^2= $C(CH_3)_3$] in 90% combined yield. These two products were separated by column chromatography using ether:hexane (8:2 v/v) as eluant to yield **193b** and **237b** in 80% and 20% yields, respectively. There are two chiral centers present in (**193a**, **193b** and **237b**) which are likely comprised of a mixture of four diastereomers (RR, SS, RS, SR). An attempt to separate the two diastereomers [RR(SS), RS(SR)] of (**193a, 193b**) by silica gel tlc using ether:hexane (7:3, or 8:2 v/v) as development solvent was unsuccessful, although the ^{1}H nmr spectrum of (**193a, 193b**) showed the presence of two different diastereomers [possibly RR(SS) and RS(SR) in a ratio of 1:1] as summarized in Table 19. Two diastereomers of **237b** were separated by preparative tlc chromatography using ether:hexane (8:2 v/v) as development solvent. Extraction of the bands having R_f= 0.55 and R_f= 0.3 with methanol provided two pure diastereomers (**237b'** and **237b''**) which were characterized by ^{1}H nmr as summarized in Table 19. The ir spectrum (cm^{-1}) showed free OH absorptions at 3427 and 3414 for (**193a** and **193b**), and an NH absorption at 3336 for (**237b'** and **237b''**). Further reaction of (**193a**) with 4-chloroquinoline in DMF in the presence of NaH afforded (**239**) which was hydrolyzed with 1.5 N HCl to yield (**233a**) as a white solid in 92% yield. The physical data for (**233a**) is presented in Table 20, and the ^{1}H nmr and ir spectroscopic data are summarized in Table 21. The physical, ^{1}H nmr and ir spectroscopic data for (**233a**) prepared by method B in Scheme 24 are identical to the product prepared by method A in Scheme 23.

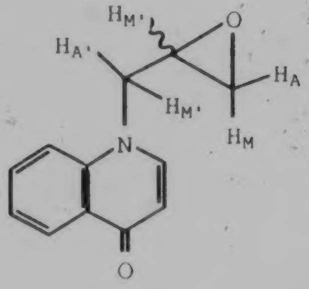
Table 18. Ir[a,b] and ^1H nmr[c] spectral data for (R,S)- 1-(quinol-4-yloxy)-2,3-epoxypropane (**231a**), (S)- 1-(quinol-4-yloxy)-2,3-epoxypropane (**231a'**) and (R,S)-1-[1-(1,4-dihydroquinolin-4-one)]-2,3-epoxypropane (**232a**).



(R,S)-**231a**



(S)-**231a'**



(R,S)-**232a**

Compd.	ir (cm^{-1})	^1H nmr δ (ppm)
231a	1250 (oxirane C-O)[a]	2.91 (d, J_{vic}= 1.9 Hz of d, J_{gem}= 4.8 Hz, 1H, H_A); 3.03 (d, J_{vic}= 4.8 Hz of d, J_{gem}= 4.8 Hz, 1H, H_M); 3.55 (m, 1H, H_X); 4.19 (d, J_{vic}= 5.8 Hz of d, J_{gem}= 10.6 Hz, 1H, $H_{A'}$); 4.53 (d, J_{vic}= 2.9 Hz of d, J_{gem}= 10.6 Hz, 1H, $H_{M'}$); 6.78 (d, $J_{2,3}$= 5.0 Hz, 1H, quinolyl H-3); 7.58 (d, $J_{6,7}$= 7.7 Hz of d, $J_{7,8}$= 7.7 Hz of d, $J_{5,7}$= 1.7 Hz, 1H, quinolyl H-7); 7.77 (d, $J_{5,6}$= 7.7 Hz of d, $J_{6,7}$= 7.7 Hz of d, $J_{6,8}$= 1.7 Hz, 1H, quinolyl H-6); 8.11 (d, $J_{5,6}$= 7.7 Hz of d, $J_{5,7}$= 1.7 Hz, 1H, quinolyl H-5); 8.31 (d,

Table 18. (cont.)

		$J_{7,8}$= 7.7 Hz of d, $J_{6;8}$= 1.7 Hz, 1H, quinolyl H-8); 8.81 (d, $J_{2,3}$= 5.0 Hz, 1H, quinolyl H-2).
231a'	1250 (oxirane C-O)[a]	2.91 (d, J_{vic}= 2.88 Hz of d, J_{gem}= 4.81 Hz, 1H, H_A); 3.03 (d, J_{vic}= 4.81 Hz of d, J_{gem}= 4.81 Hz, 1H, H_M); 3.55 (m, 1H, H_X); 4.19 (d, J_{vic}= 5.77 Hz of d, J_{gem}= 10.54 Hz, 1H, $H_{A'}$); 4.54 (d, J_{vic}= 3.84 Hz of d, J_{gem}= 11.54 Hz, 1H, $H_{M'}$); 6.79 (d, $J_{2,3}$= 5.62 Hz, 1H, quinolyl H-3); 7.58 (d, $J_{6,7}$= 6.75 Hz of d, $J_{7,8}$= 6.75 Hz of d, $J_{5,7}$= 1.68 Hz, 1H, quinolyl H-7); 7.77 (d, $J_{5,6}$= 6.75 Hz of d, $J_{6,7}$= 6.75 Hz of d, $J_{6,8}$= 1.68 Hz, 1H, quinolyl H-6); 8.11 (d, $J_{5,6}$= 6.75 Hz of d, $J_{5,7}$= 1.68 Hz, 1H, quinolyl H-5); 8.31 (d, $J_{7,8}$= 6.75 Hz of d, $J_{6,8}$= 1.68 Hz, 1H, quinolyl H-8); 8.81 (d, $J_{2,3}$= 5.62 Hz, 1H, quinolyl H-2).
232a	1250 (oxirane C-O), 1633(C=O)[b]	2.57 (d, J_{vic}= 2.2 Hz of d, J_{gem}= 4.3 Hz, 1H, H_A); 2.92 (d, J_{vic}= 4.3 Hz of d, J_{gem}= 4.3 Hz, 1H, H_M); 3.39 (m, 1H, H_X); 4.18 (d, J_{vic}= 6.5 Hz of d, J_{gem}= 16.2 Hz, 1H, $H_{A'}$); 4.54 (d, J_{vic}= 2.2 Hz of d, J_{gem}= 16.2 Hz, 1H, $H_{M'}$); 6.30 (d, $J_{2,3}$= 7.7 Hz, 1H, quinolinone H-3); 7.44 (d, $J_{5,6}$= 8.4 Hz of d, $J_{6,7}$= 6.4 Hz, 1H, quinolinone H-6); 7.55 (d, $J_{7,8}$= 7.7 Hz, 1H, quinolinone H-8); 7.58 (d, $J_{2,3}$= 7.7 Hz, 1H, quinolinone H-2);

Table 18. (cont.)

7.73 (d, $J_{6,7}$= 6.4 Hz of d, $J_{7,8}$= 7.7 Hz of d, $J_{5,7}$= 1.8 Hz, 1H, quinolinone H-7); 8.5 (d, $J_{5,6}$= 8.4 Hz of d, $J_{5,7}$= 1.8 Hz, 1H, quinolinone H-5).

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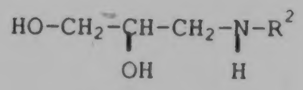
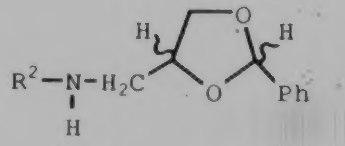
[a]Film , [b]KBr . [c]The spectrum was determined in $CDCl_3$

Table 19. Ir[a] and ^{1}H nmr[b] spectral data for 3-isopropyl (or t-butyl)amino-1,2-propanediol (**236a,b**), 2-phenyl-5-(t-butylaminomethyl)-1,3-dioxolidines (**237 b', 237 b''**), 2-phenyl-3-isopropyl (or t-butyl)-5-(hydroxymethyl)oxazolidines (**193a**, **193b**).

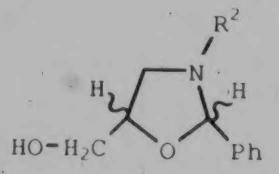


$HO{-}CH_2{-}\underset{OH}{CH}{-}CH_2{-}\underset{H}{N}{-}R^2$

236 (a,b)



237 (b', b'')



193 (a,b)

a, $R^2 = CH(CH_3)_2$; **b**, $R^2 = C(CH_3)_3$

Compd.	ir (cm^{-1})	^{1}H nmr δ (ppm)
236a	3254 (OH)	1.02 and 1.03 [two d, J= 6.6 Hz, 6H total, NH-CH($\underline{CH}_3$)$_2$]; 2.56 (d, J_{gem}= 12.5 Hz, of d, J_{vic}= 8.8 Hz, 1H, -CH(OH)-C$\underline{H}$H^1-NH-); 2.74 (d, J_{gem}= 12.5 Hz, of d, J_{vic}= 3.7 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-); 2.85 [heptet, J= 6.6 Hz, 1H, NH-C$\underline{H}$(CH$_3$)$_2$]; 3.52 [d, J_{gem}= 8.6 Hz, of d, J_{vic}= 4.8 Hz, 1H, HO-C$\underline{H}$H^1-CH(OH)-]; 3.62 [d, J_{gem}= 8.6 Hz, of d, J_{vic}= 3.3 Hz, 1H, HO-CH$\underline{H}^1$-CH(OH)-]; 3.8 [m, 1H, C$\underline{H}$(OH)]; 4.08 (br s, 3H, 2 O$\underline{H}$ and N$\underline{H}$, exchange with deuterium oxide).

Table 19. (cont.)

236b	3254 (OH)	1.12 (s, 9H, t-Bu); 2.63 (d, J_{gem}= 11.8 Hz, of d, J_{vic}= 6.7 Hz, 1H, -CH(OH)-C$\underline{H}$H^1-NH-); 2.77 (d, J_{gem}= 11.8 Hz, of d, J_{vic}= 4.4 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-); 3.42 (br s, 3H, 2 -OH, -NH- exchange with deuterium oxide); 3.6 [d, J_{gem}= 11.1 Hz, of d, J_{vic}= 5.2 Hz, 1H, HO-C$\underline{H}$H^1-CH(OH)-]; 3.71 [d, J_{gem}= 11.1 Hz of d, J_{vic}= 3.7 Hz, 1H, HO-CH$\underline{H}^1$-CH(OH)-]; 3.75 [m, 1H, HO-CH_2-$\underline{CH}$(OH)-].
193a	3427 (OH)	0.9 (m, 6H , NH-CH($\underline{CH_3}$)$_2$]; 2.0 (br s, 1H, OH exchanges with deuterium oxide); 2.7, 3.04 and 3.24 (three m, 2H total, oxazolidinyl H-4); 2.78 [m, 1H, NH-C$\underline{H}$(CH_3)$_2$]; 3.66 (m, 2H, HO-$\underline{CH_2}$-5- oxazolidinyl); 4.24 and 4.3 (two m (1:1 in ratio), 1H total, oxazolidinyl H-5); 5.09 and 5.12 [two s (1:1 ratio)], 1H total, oxazolidinyl H-2); 7.36 and 7.52 (two m, 5H total, phenyl hydrogens).
193b	3418 (OH)	1.05 and 1.09 (two s, (ratio 6:4), 9H total, t-Bu); 1.95 (br s, 1H, OH exchanges with deuterium oxide); 2.96, 3.15 and 3.32 (three m, 2H total, oxazolidinyl H-4); 3.49, 3.66 and 3.8 (three m, 2H total, HO-$\underline{CH_2}$-oxazolidinyl); 4.11 (m, 1H, oxazolidinyl H-5); 5.56 and 5.6 [two s (6:4 ratio), 1H, oxazolidinyl H-2]; 7.32 (m, 3H, phenyl *meta* -, *para* -hydrogens); 7.57 (m, 2H, phenyl *ortho* -hydrogens).

Table 19. (cont.)

237b'	3336 (NH)	1.14 (s, 9H, t-Bu); 1.45 (br s, 1H, N$\underline{H}$, exchanges with deuterium oxide); 2.71 (d, J_{vic}= 4.7 Hz of d, J_{gem}= 11.2 Hz, 1H, 1,3-dioxolidinyl $\underline{H}H^1$-4); 2.87 (d, J_{vic}= 7.5 Hz of d, J_{gem}= 11.2 Hz, 1H, 1,3-dioxolidinyl $H\underline{H}^1$-4); 3.78 (d, J_{vic}= 6.5 Hz of d, J_{gem}= 7.9 Hz, 1H, -NH-C$\underline{H}H^1$-1,3-dioxolidinyl); 4.27 (d, J_{vic}= 7.0 Hz of d, $J_{gem.}$= 7.9 Hz, -NH-CH$\underline{H}^1$-1,3-dioxolidinyl); 4.38 (m, 1H, 1,3-dioxolidinyl H-5); 5.96 (s, 1H, 1,3-dioxzolidinyl H-2); 7.40 (m, 3H, phenyl *meta* - and *para* -hydrogens); 7.51 (m, 2H, phenyl *ortho* -hydrogens).
237b''	3336 (NH)	1.10 (s, 9H, t-Bu); 1.15 (br s, 1H, N$\underline{H}$, exchanges with deuterium oxide); 2.74 (d, J_{vic}= 4.5 Hz of d, J_{gem}= 12.1 Hz, 1H, 1,3-dioxolidinyl $\underline{H}H^1$-4); 2.84 (d, J_{vic}= 7.6 Hz of d, J_{gem}= 12.1 Hz, 1H, 1,3-dioxolidinyl $H\underline{H}^1$-4); 3.87 (d, J_{vic}= 5.8 Hz of d, J_{gem}= 7.1, 1H, -NH-C$\underline{H}H^1$-1,3-dioxolidinyl); 4.12 (d, J_{vic}= 7.12 Hz of d, J_{gem}= 7.1 Hz, 1H, -NH-CH$\underline{H}^1$-1,3-dioxolidinyl); 4.32 (m, 1H, 1,3-dioxolidinyl H-5); 5.82 (s, 1H, 1,3-dioxolidinyl H-2); 7.39 (m, 3H, phenyl *meta* -, *para* - hydrogens); 7.52 (m, 2H, phenyl *ortho* -hydrogens).

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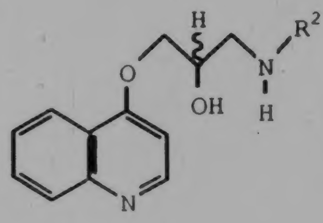
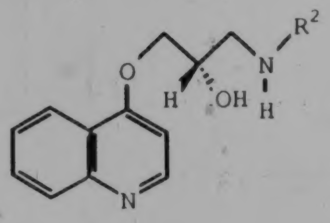
[a] KBr . [b] The spectrum was determined in $CDCl_3$

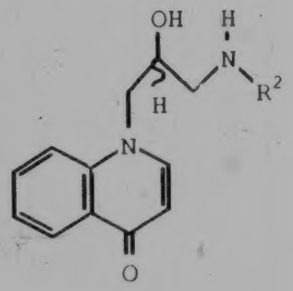
Table 20. Physical data for (R,S)-1-(quinol-4-yloxy)-3-alkylamino-2-propanol (**233a**)[a,b], (S)-1-(quinol-4-yloxy)-3-alkylamino-2-propanol (**233a'**)[a], (R,S)-1-[1-(1,4-dihydroquinolin-4-one)]-3-isopropylamino-2-propanol (**234a**)[a], and (R,S)-1-(quinol-2-yloxy)-3-alkylamino-2-propanols (**242a,b**)[b].



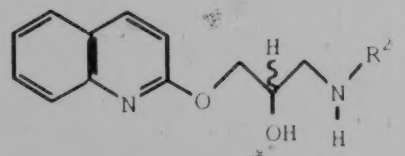
(R,S)-**233a**



(S)-**233a'**



(R,S)-**234a**



242(a,b)

a, R^2= i-Pr ; **b**, R^2= t-Bu

Compd.	R^2	R_f	Yield, %	MP,°C	Formula	Microanalyses: Found (Calcd.) %C	%H	%N
233a	$CH(CH_3)_2$	0.50[c]	92	61-62	$C_{15}H_{20}N_2O_2$	68.99	7.79	10.67
						(69.20)	(7.74)	(10.76)
233a'[d]	$CH(CH_3)_2$	0.43[e]	92	207	$C_{15}H_{22}N_2O_2Cl_2$, 1/2 H_2O	52.86	6.71	8.12
						(52.59)	(6.71)	(8.18)

Table 20. (cont.)

Compd.	R^2	R_f	Yield, %	MP,°C	Formula	%C	%H	%N
234a[f]	$CH(CH_3)_2$	0.38[g]	95	127	$C_{15}H_{20}N_2O_2$	68.45	7.64	10.45
						(69.20)	(7.74)	(10.76)
242a	$CH(CH_3)_2$	0.60[h]	90	130-131	$C_{15}H_{20}N_2O_2$	69.02	7.82	10.64
						(69.20)	(7.74)	(10.76)
242b	$C(CH_3)_3$	0.65[h]	91	101-102	$C_{16}H_{22}N_2O_2$	70.02	7.98	10.21
						(70.03)	(8.08)	(10.21)

[a] Prepared by method A in Scheme 24. [b] Prepared by method B in Scheme 25.

[c] Ether:methanol (2:1 v/v) as tlc development solvent .

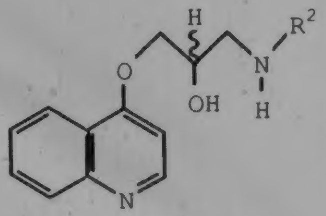
[d] The dihydrochloride salt of (**233a'**) was prepared since the free base was an oil, that had an R_f of 0.43, which did not give acceptable microanalytical data.

[e] Ether:ethanol (8:2 v/v) as tlc development solvent .

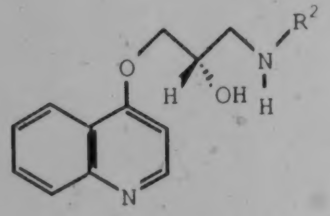
[f] The correct microanalytical data for the dihydrochloride salt for (**234a**) will be presented in experimental section.

[g] Ether:ethanol (7:3 v/v), [h] ether:ethanol (8:2 v/v) as tlc development solvent for free base.

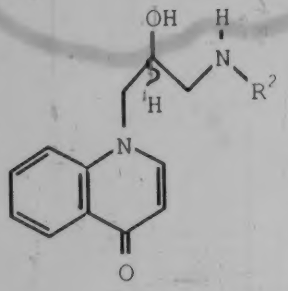
Table 21. Ir[a] and ^{1}H nmr[b] spectral data for (R,S)-1-(quinol-4-yloxy)-3-alkylamino-2-propanol (**233a**)[c,d], (S)-1-(quinol-4-yloxy)-3-alkylamino-2-propanol (**233a'**)[c], (R,S)-1-[1-(1,4-dihydroquinolin-4-one)]-3-isopropylamino-2-propanol (**234a**)[c] and (S)-1-[1-(1,4-dihydroquinolin-4-one)]-3-isopropylamino-2-propanol (**234a'**)[illegible] and (R,S)-1-(quinol-2-yloxy)-3-alkylamino-2-propanols (**242a,b**)[d].



(R,S)-**233a**

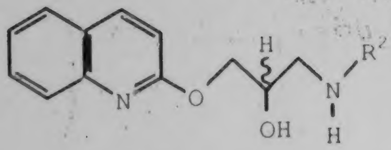


(S)-**233a'**



(R,S)-**234a**

(S)-**234a'**



242(a,b)

a, R^2= i-Pr ; **b**, R^2= t-Bu

Compd.	ir (cm^{-1})(OH, NH)	^{1}H nmr δ (ppm)
233a	3181	1.11 [d, J= 5.63 Hz, 6H, -CH($\underline{CH}_3$)$_2$]; 2.65 (br s, 2H, -O$\underline{H}$, -N$\underline{H}$-, exchange with deuterium oxide); 2.85 (m, 2H, -$\underline{CH}$(CH$_3$)$_2$; CH(OH)-C$\underline{H}$H^1-NH-); 2.99 (d, J_{vic}= 3.52 Hz of d, J_{gem}= 11.44 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-); 4.20 [m, 3H, -O-CH$_2$-$\underline{CH}$(OH)-; -O-$\underline{CH}_2$-CH(OH)-]; 6.70 (d, $J_{2,3}$= 5.45 Hz, 1H, quinolyl H-3); 7.47 (d, $J_{6,7}$= 7.63 Hz

Table 21. (cont.)

		of d, $J_{7,8}$= 7.63 Hz of d, $J_{5,7}$= 1.09 Hz, 1H, quinolyl H-7); 7.68 (d, $J_{5,6}$= 8.72 Hz of d, $J_{6,7}$= 7.63 Hz of d, $J_{6,8}$= 1.09 Hz, 1H, quinolyl H-6); 8.02 (d, $J_{5,6}$= 8.72 Hz of d, $J_{5,7}$= 1.09 Hz, 1H, quinolyl H-5); 8.15 (d, $J_{7,8}$= 7.63 Hz of d, $J_{6,8}$= 1.08 Hz, 1H, quinolyl H-8); 8.69 (d, $J_{2,3}$= 5.45 Hz, 1H, quinolinyl H-2).
233a'e	3312	1.32 [m, 6H, -CH($\underline{CH}_3$)$_2$]; 3.18 and 3.32 [two m, 2H total, CH(OH)-$\underline{CH}_2$-NH-]; 3.54 [m, 1H, -$\underline{CH}$(CH$_3$)$_2$]; 3.54 (br s, 1H, -O$\underline{H}$, exchanges with deuterium oxide); 4.6 (m, 3H, -O-$\underline{CH}_2$-CH(OH)-, -O-CH$_2$-$\underline{CH}$(OH)-]; 6.29 (br s, 1H, -N$\underline{H}$, exchanges with deuterium oxide); 7.59 (d, $J_{2,3}$= 6.75 Hz, 1H, quinolyl H-3); 7.92 (d, $J_{5,6}$= 8.73 Hz of d, $J_{6,7}$= 8.73 Hz of d, $J_{6,8}$= 1.45 Hz, 1H, quinolyl H-6); 8.14 (d, $J_{6,7}$= 8.73 Hz of d, $J_{7,8}$= 8.73 Hz of d, $J_{5,7}$= 1.45 Hz, 1H, quinolyl H-7); 8.33 (d, $J_{5,6}$= 8.73 Hz of d, $J_{5,7}$= 1.45 Hz, 1H, quinolyl H-5); 8.58 (d, $J_{7,8}$= 8.73 Hz of d, $J_{6,8}$= 1.45 Hz, 1H, quinolyl H-8); 8.90 (br s, 1H, -N$\underline{H}$, exchanges with deuterium oxide); 9.23 (d, $J_{2,3}$= 6.79 Hz, 1H, quinolinyl H-2); 9.33 br s, 1H, -N$\underline{H}$, exchanges with deuterium oxide).
234a	3353	1.12 [d, J= 7.50 Hz, 6H, -CH($\underline{CH}_3$)$_2$]; 2.7 (d; J_{vic}= 7.55 Hz of d, J_{gem}= 12.0 Hz, 1H, CH(OH)-C$\underline{H}$H^1-NH-); 2.88 [m, 1H, -$\underline{CH}$(CH$_3$)$_2$]; 2.91 [d, J_{vic}= 4.53 Hz of d, J_{gem}=

Table 21. (cont.)

		12.0 Hz, 1H, CH(OH)-CH$\underline{H}^{1}$-NH-]; 3.94 (d, J_{vic}= 9.06 Hz of d, J_{gem}= 13.59 Hz, 1H, 1-quinolone-C$\underline{H}$H^{1}-CH(OH)-]; 4.21 [m, 1H, -C$\underline{H}$(OH)-]; 4.38 [d, J_{vic}= 3.96 Hz of d, J_{gem}= 13.59 Hz, 1H, 1-quinolone-C$\underline{H}$H^{1}-CH(OH)-]; 5.92 (d, $J_{2,3}$= 6.93 Hz, 1H, quinolone H-3); 7.23 (d, $J_{5,6}$= 7.92 Hz of d, $J_{6,7}$= 7.92 Hz, 1H, quinolone H-6); 7.52 (d, $J_{7,8}$= 7.92 Hz, 1H, quinolone H-8); 7.61 (d, $J_{2,3}$= 6.93 Hz, 1H, quinolone H-2); 7.62 (d, $J_{6,7}$= 7.92 Hz of d, $J_{7,8}$= 7.92 Hz of d, $J_{5,7}$= 1.98 Hz, 1H, quinolone H-7); 8.04 (d, $J_{5,6}$= 7.92 Hz of d, $J_{5,7}$= 1.98 Hz, 1H, quinolone H-5). Note: The OH and NH resonances were not visible in the spectrum probably due to the fact that they are very broad.
234a'	3353	1.12 [d, J=7.42 Hz, 6H, -CH(C$\underline{H}_{3}$)$_{2}$]; 2.7 (d, J_{vic}= 7.42 Hz of d, J_{gem}= 11.13 Hz, 1H, CH(OH)-C$\underline{H}$H^{1}-NH-); 2.88 [m, 1H, -$\underline{CH}$(CH$_{3}$)$_{2}$]; 2.93 [d, J_{vic}= 3.7 Hz of d, J_{gem}= 11.13 Hz, 1H, CH(OH)-CH$\underline{H}^{1}$-NH-]; 3.95 (d, J_{vic}= 9.27 Hz of d, J_{gem}= 14.84 Hz, 1H, 1-quinolone-C$\underline{H}$H^{1}-CH(OH)-]; 4.21 [m, 1H, -C$\underline{H}$(OH)-]; 4.38 [d, J_{vic}= 3.71 Hz of d, J_{gem}= 14.84 Hz, 1H, 1-quinolone-C$\underline{H}$H^{1}-CH(OH)-]; 5.98 (d, $J_{2,3}$= 8.33 Hz, 1H, quinolone H-3); 7.26 (d, $J_{5,6}$= 7.73 Hz of d, $J_{6,7}$= 7.73 Hz, 1H, quinolone H-6); 7.51

Table 21. (cont.)

		(d, $J_{7,8}$= 7.73 Hz, 1H, quinolone H-8); 7.62 (d, $J_{2,3}$= 8.33 Hz, 1H, quinolone H-2); 7.63 (d, $J_{6,7}$= 7.73 Hz of d, $J_{7,8}$= 7.73 Hz of d, $J_{5,7}$= 1.2 Hz, , 1H, quinolone H-7); 8.12 (d, $J_{5,6}$= 7.73 Hz of d, $J_{5,7}$= 1.2 Hz, 1H, quinolone H-5). Note: The OH and NH resonances were not visible in the spectrum probably due to the fact that they are very broad.
242a	3266	1.09 and 1.10 [two d, J= 6 Hz, 3H each, $-CH(C\underline{H}_3)_2$]; 2.75 (d, J_{vic}= 8.10 Hz of d, J_{gem}= 11.34 Hz, 1H, $CH(OH)-C\underline{H}H^1-NH-$); 2.86 [m, 1H, $-\underline{CH}(CH_3)_2$]; 2.90 (d, J_{vic}= 4.17 Hz of d, J_{gem}= 11.34 Hz, 1H, $-CH(OH)-CH\underline{H}^1-NH-$); 2.98 (br s, 2H, $-O\underline{H}$ and $-N\underline{H}-$, exchange with deuterium oxide); 4.13 [m, 1H, $HO-CH_2-\underline{CH}(OH)-$]; 4.54 [d, J_{vic}= 5.49 Hz of d, J_{gem}= 10.98 Hz, 1H, $-O-C\underline{H}H^1-CH(OH)-$]; 4.64 (d, J_{vic}= 3.66 Hz of d, J_{gem}= 10.98Hz, 1H, $-O-CH\underline{H}^1-CH(OH)-$]; 7.00 (d, $J_{3,4}$= 8.93 Hz, 1H, quinolyl H-3); 7.42 (d, $J_{5,6}$= 8.23 Hz of d, $J_{6,7}$= 8.23 Hz of d, $J_{6,8}$= 0.91 Hz, 1H, quinolyl H-6); 7.66 (d, $J_{6,7}$= 8.23 Hz of d, $J_{7,8}$= 8.23 Hz of d, $J_{5,7}$= 1.83 Hz , 1H, quinolyl H-7); 7.76 (d, $J_{5,6}$= 8.23 Hz of d, $J_{5,7}$= 1.83 Hz, 1H, quinolyl H-5); 7.85 (d, $J_{7,8}$= 8.23 Hz of d, $J_{6,8}$= 0.91 Hz, 1H, quinolyl H-8); 8.05 (d, $J_{3,4}$= 8.93 Hz, 1H, quinolyl H-4).

Table 21. (cont.)

242b	3143	1.13 (s, 9H, t-Bu); 2.70 (d, J_{vic}= 7.28 Hz of d, J_{gem}= 11.76 Hz, 1H, CH(OH)-C$\underline{H}$H^1-NH-); 2.81 (d, J_{vic}= 4.48 Hz of d, J_{gem}= 11.76 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-); 3.0 (br s, 2H, -O$\underline{H}$, -N$\underline{H}$-, exchange with deuterium oxide); 4.03 [m, 1H, HO-CH$_2$-C$\underline{H}$(OH)-]; 4.51 [d, $J_{vic.}$= 5.60 Hz of d, $J_{gem.}$= 11.20 Hz, -O-C$\underline{H}$H^1-CH(OH)-]; 4.63 (d, J_{vic}= 3.36 Hz of d, J_{gem}= 11.2 Hz, 1H, -O-CH$\underline{H}^1$-CH(OH)-]; 6.99 (d, $J_{3,4}$= 8.93 Hz, 1H, quinolyl H-3); 7.43 (d, $J_{5,6}$= 8.0 Hz of d, $J_{6,7}$= 8.0 Hz of d, $J_{6,8}$= 1.54 Hz, 1H, quinolyl H-6); 7.66 (d, $J_{6,7}$= 8.0 Hz of d, $J_{7,8}$= 8.0 Hz of d, $J_{5,7}$= 1.54 Hz , 1H, quinolyl H-7); 7.77 (d, $J_{5,6}$= 8.0 Hz of d, $J_{5,7}$= 1.54 Hz, 1H, quinolyl H-5); 7.86 (d, $J_{7,8}$= 8.0 Hz of d, $J_{6,8}$= 1.54 Hz, 1H, quinolyl H-8); 8.05 (d, $J_{3,4}$= 8.93 Hz, 1H, quinolyl H-4).

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[a] KBr. [b] All spectra were determined in CDCl$_3$ except for the spectrum of (R,S)-(**234a**) which was determined in CDCl$_3$/DMSO-d$_6$.

[c] Prepared by method A in Scheme 24. [d] Prepared by B in Scheme 25.

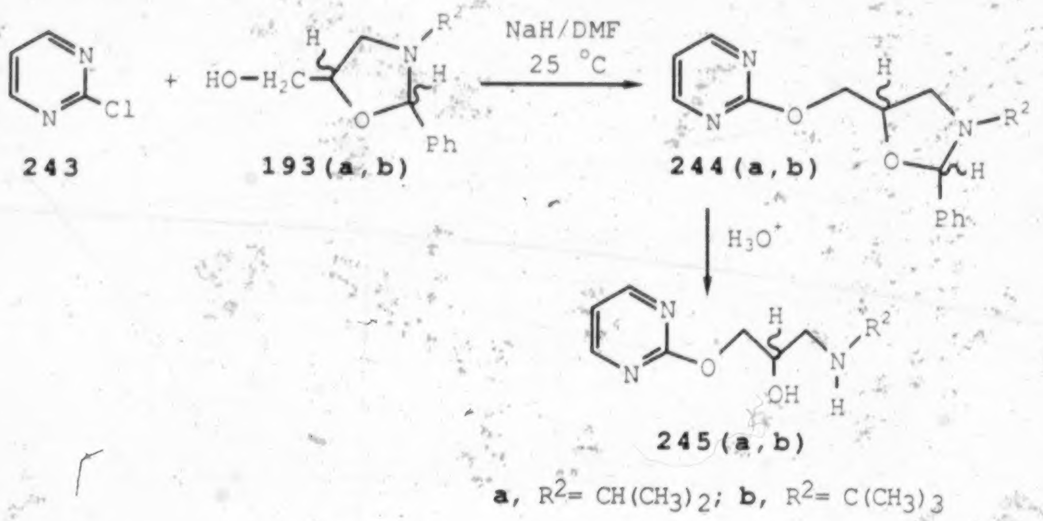
[e] The dihydrochloride salt of (**233a'**) was prepared since the free base was an oil which did not give acceptable microanalytical data. The ^{1}H nmr spectrum was determined in DMSO-d$_6$.

3.4.2.4.0 SYNTHESIS OF (R,S)-1-(QUINOL-2-YLOXY)-3-ISOPROPYLAMINO-2-PROPANOL AND (R,S)-1-(QUINOL-2-YLOXY)-3-t-BUTYLAMINO-2-PROPANOL.

A similar reaction of (**193a** or **193b**) with 2-chloroquinoline gave (**242a** or **242b**) in 90-91% yield. The physical data for (**242a**, **242b**) are presented in Table 20, and the ^{1}H nmr and ir spectroscopic data are summarized in Table 21. The ^{1}H nmr spectra for (**242a**, **242b**) indicated that the chiral carbon (CH_XOH) causes the adjacent methylene protons to be magnetically and chemically non-equivalent as illustrated in Figure 10, whereas the oxymethylene protons ($O-C\underline{H}_2-CH_XOH$) for (**233a**) exhibited the same chemical shift. The chemical shift for the oxymethylene protons ($O-C\underline{H}_2-CH_XOH$) of (**242a**, **242b**) is shifted to lower field than the corresponding protons in (**233a**), since the former methylene group is attached to a 2-quinolyl substituent (**242a**, **242b**) that has a stronger deshielding effect than the 4-quinolyl substituent present in (**233a**). The ir spectra (cm^{-1}) revealed a NH absorption at 3266 for (**242a**) and a hydroxyl absorption at 3266, 3143 and 3181 for (**242a**, **242b** and **233a**), respectively which showed strong hydrogen bonding as illustrated in Figure 12.

3.4.3.0.0 SYNTHESIS (R,S)-1-(PYRIMIDIN-2-YLOXY)-3-ALKYLAMINO-2-PROPANOLS.

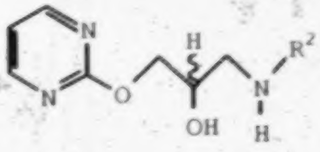
Many substituted pyridines possess vasodilator activity[364-368]. A combination of vasodilator and β-adrenergic antagonist activities have been reported for some pyridine compounds such as (S)-1-[3-cyano-2-pyridylyloxy)]-3-t-butylamino-2-propanol (**112**)[382]. Pyrimidine could be an isostere of 3-cyanc or 3-nitropyridine[382]. A study was therefore initiated to replace the 3-cyanopyridine ring of (**112**) by a 2-pyrimidyl ring to determine the effect of the second nitrogen atom in the heteroaryl moiety upon β-adrenergic antagonist activity. Reaction of 2-chloropyrimidine (**243**) with (**193a,b**) in DMF in the presence of NaH afforded (**244a,b**) in 92-95% yields, which were hydrolyzed using 1.5 N HCl to give the target compounds (**245a,b**) in 90-92% yield as outlined in Scheme 25.



Scheme 25. Synthesis of (2R,2S)-1-(pyrimidin-2-yloxy)-3-isopropyl (or t-butyl)amino-2-propanols (**245a,b**).

The physical data for (**245a,b**) are presented in Table 22. The structures assigned to (**244a,b** and **245a,b**) in Scheme 25 were consistent with their ir and ^1H nmr spectral data which are summarized in Table 23. The ^1H nmr spectrum showed the presence of two different diastereomers [RR(SS) and RS(SR)] in a ratio 1:1 for (**244a**) and 1:2 for (**244b**), which were obtained after purification by column chromatography.

Table 22. Physical data for (R,S)-1-(pyrimidin-2-yloxy)-3-isopropyl(or t-butyl)amino-2-propanols.

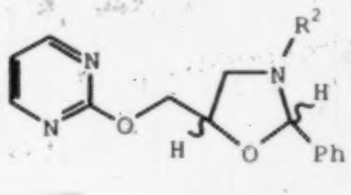


245 (a,b)

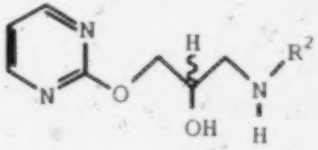
Compd.	R^2	R_f	Yield, %	MP,°C	Formula	Microanalyses: Found (Calcd.) %C	%H	%N
245a	$CH(CH_3)_2$	0.3[a]	90	52	$C_{10}H_{17}N_3O_2$	56.58 (56.85)	8.11 (8.11)	19.77 (19.89)
245b	$C(CH_3)_3$	0.45[a]	92	82	$C_{11}H_{19}N_3O_2$	58.42 (58.64)	8.48 (8.50)	18.51 (18.65)

[a] Eher:ethanol (8:2 v/v) as development solvent.

Table 23. Ir[a] and ^{1}H nmr[b] spectral data for 2-{2-phenyl-3-isopropyl (or t-butyl)-5-(methoxy)oxazolidinyl}pyrimidines (**244a,b**); (R,S)-1-(pyrimidin-2-yloxy) -3-alkylamino-2-propanols (**245a,b**).



244(a,b)



245(a,b)

a, R^2= i-Pr; **b**, R^2= t-Bu.

Compd.	ir (cm^{-1}) (OH)	^{1}H nmr δ (ppm)
244a	1577, 1563 (C=N)	1.05 [complex m, 6H, -CH($\underline{CH}_3$)$_2$]; 2.80 (m, 1H, -$\underline{CH}$(CH$_3$)$_2$]; 2.84, 3.14, and 2.44 (three m, 2H total, oxazolidinyl H-4); 4.50 (m, 3H, -O-$\underline{CH}_2$-, oxazolidinyl H-5); 5.18 and 5.24 [two s (ratio 1:1), 1H total, oxazolidinyl H-2]; 6.94 and 6.96 (two d, $J_{4,5}$= 5.0 Hz of d, $J_{5,6}$= 5.0 Hz, 1H total, pyrimidinyl H-5); 7.34 (m, 3H, *meta* - and *para* - phenyl hydrogens); 7.53 (m, 2H, phenyl *ortho* -phenyl hydrogens); 8.50 and 8.51 [two d, $J_{4,5}$= 5.0 Hz, $J_{5,6}$= 5.0 Hz (ratio 1:1), 2H total, pyrimidinyl H-4 and H-6].

Table 23 (cont.)

245a	3301	1.07 and 1.08 [two d, J= 6.0 Hz, 3H each, $-CH(C\underline{H}_3)_2$]; 2.71 (d, J_{vic}= 8.0 Hz of d, J_{gem} = 12.0 Hz, 1H of $-CH(OH)-C\underline{H}H^1-NH-$); 2.80 [m, 1H of $-\underline{CH}(CH_3)_2$]; 2.86 (d, J_{vic}= 4.0 Hz of d, J_{gem}= 12.0 Hz, 1H of $-CH(OH)-CH\underline{H}^1-NH-$); 3.01 (br s, 2H, N$\underline{H}$, O$\underline{H}$, exchange with deuterium oxide); 4.13 [m, 1H, $-\underline{CH}(OH)-$]; 4.38 (m, 2H, $-O-\underline{CH_2}-CH(OH)-$]; 6.94 (d, $J_{4,5}$= 5.25 Hz of d, $J_{5,6}$= 5.25 Hz, 1H, pyrimidinyl H-5); 8.5 (d, $J_{4,5}$= $J_{5,6}$= 5.25 Hz, 2H total, pyrimidinyl H-4 and H-6).
244b	1577, 1563 (C=N)	1.08 and 1.13 [two s (ratio 1:2), 9H total, t-Bu]; 2.98, 3.34 and 3.52 (three m, 2H total, oxazolidinyl H-4); 4.13 (d, J_{gem}= 8.94 Hz of d, J_{vic}=5.96 Hz, 1H, $-O-C\underline{H}H^1-$oxazolidinyl); 4.38 (m, 1H, $-O-CH\underline{H}^1-$oxazolidinyl); 4.44 and 4.55 [two m (ratio 2:1), 1H total, oxazolidinyl H-5]; 5.65 and 5.74 (two s (rati[illegible]azolidinyl H-2); 6.93 and 6.95 (two d, $J_{4,5}$= 4.5 Hz of d, $J_{5,6}$= 4.5 Hz [illegible] total, pyrimidinyl H-5); 7.33 (m, 3H, *meta* - and *para* -phenyl hydrogens); 7.62 (m, [illegible], phenyl *ortho* hydrogens); 8.52 (d, $J_{4,5}$= $J_{5,6}$= 4.5 Hz, 2H total, perimidinyl H-4 [illegible]d H-6).

Table 23 (cont.)

245b	3319	1.11 (s, 9H, t-Bu); 2.71 (d, J_{vic}= 8.08 Hz of d, J_{gem}= 11.42 Hz, 1H of -CH(OH)-C$\underline{H}$H^1-NH-); 2.84 (d, J_{vic}= 4.27 Hz of d, J_{gem}= 11.42 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-); 3.01 (br s, 2H, -O$\underline{H}$ and -N$\underline{H}$- exchange with deuterium oxide); 4.06 [m, 1H -$\underline{CH}$(OH)-]; 4.40 (d, J= 5.70 Hz, 2H, pyrimidinyl-O-$\underline{CH_2}$-CH(OH)-]; 6.96 (t, $J_{4,5}$= $J_{5,6}$= 4.86 Hz, 1H, pyrimidinyl H-5); 8.53 (d, $J_{4,5}$= $J_{5,6}$= 4.86 Hz, 2H, perimidinyl H-4 and H-6).

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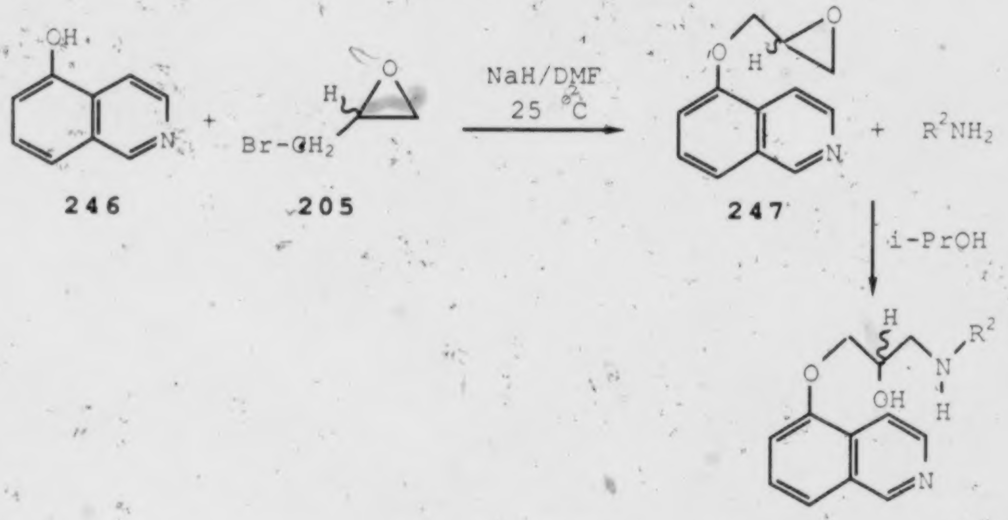
[a] KBr .

[b] The spectrum was determined in $CDCl_3$.

The ratio of the two different diastereomers [RR(SS) and RS(SR)] for (**244a**) and (**244b**) was calculated from the integrals of the respective absorptions for the oxazolidinyl H-2 and H-5 protons. These ratios were similar to the ratios of starting materials (**193a,b**). The ir spectrum (cm^{-1}) indicated the presence of a hydroxyl absorption at 3301-3319 for (**245a,b**).

3.4.4.0.0 SYNTHESIS OF 1-(ISOQUINOL-5-YLOXY)-3-ALKYLAMINO-2-PROPANOLS.

Previously, a series of highly potent and selective β_1/β_2 adrenergic antagonists were investigated where the heteroaryl moiety was a 5-quinolinyl group. It was therefore of interest to investigate the effect which the position of the nitrogen atom in the heteroaryl moiety has upon activity. This study was initiated to determine the effect of a 5-isoquinolinyl group upon β-adrenergic antagonist activity. Reaction of 5-hydroxyisoquinoline (**246**) with epibromohydrin (**205**) in DMF in the presence of NaH afforded 1-(isoquinol-5-yloxy)-2,3-epoxypropane (**247**) in 85% yield. The subsequent reaction of (**247**) with various alkylamines gave 1-(isoquinol-5-yloxy)-3-alkyl(aryl)amino-2-propanols (**248-251**) in 90-98% yield as outlined in Scheme 26. The physical data for (**247-251**) are presented in Table 24. The structures assigned to (**247-251**) in Scheme 26 were consistent with their ir and ^{1}H nmr spectral data which are summarized in Table 25. The ^{1}H nmr spectrum for the oxirane (**247**) indicated that the C-1 and C-3 methylene protons were chemically and magnetically non-equivalent and appeared as a typical AMX pattern shown previously in Figure 11.



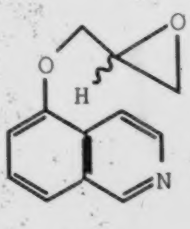
248, R^2= $CH(CH_3)_2$; **249**, R^2= $C(CH_3)_3$;

250, R^2= Cyclohexyl; **251**, R^2= $(CH_2)_3$-Ph.

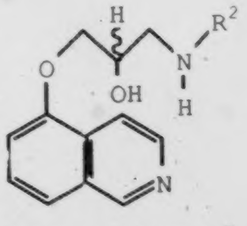
Scheme 26. Synthetic method for the synthesis of (2R,2S)-1-(isoquinol-5-yloxy)-3-alkylamino-2-propanols (**248-251**).

In contrast, the ^{1}H nmr spectra for (**248-251**) displayed the same chemical shift for the methylene protons [O-C$\underline{H}_2$-CH(OH)-], but chemical and magnetic non-equivalence for the methylene protons [-CH(OH)-C$\underline{H}_2$NH-]. The ir spectra (cm^{-1}) indicated the presence of an OH absorption in the 3082-3377 range for (**248-251**) and a NH absorption at 3238-3254 for (**248-250**). The order of hydrogen bonding strength is as explained previously in Figure 12 for similar compounds. The high resolution mass spectrum for (**251**) displayed a molecular ion at m/z 336.1844 ($C_{21}H_{24}N_2O_2$, 3.73%). Loss of an epoxide radical from the molecular ion gave rise to the base peak at m/z 145.0529 (($C_9H_7NO^+$, 100%) as shown in Scheme 20 Path A.

Table 24. Physical data for (2R,2S)-1-(isoquinol-5-yloxy) -2,3-epoxypropane (**247**) and (2R,2S)-1-(isoquinol-5-yloxy) -3-alkylamino-2-propanols (**248-251**).



247



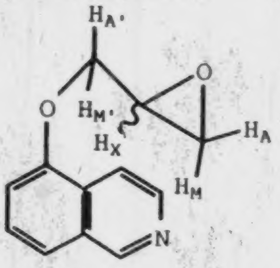
248, R^2= $CH(CH_3)_2$; **249**, R^2= $C(CH_3)_3$;

250, R^2= Cyclohexyl; **251**, R^2= $(CH_2)_3$-Ph.

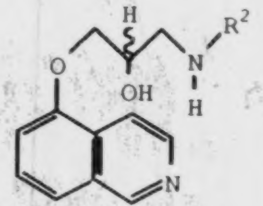
Compd.	R_f	Yield,%	MP,°C	Formula	Exact mass		Microanalyses: Found (Calcd.)		
					Calcd.	Found	%C	%H	%N
247	0.56[a]	85	oil	$C_{12}H_{20}N_2O_2$			71.71 (71.62)	5.33 (5.51)	6.97 (6.96)
248	0.42[b]	98	135	$C_{15}H_{20}N_2O_2$			69.08 (69.20)	7.53 (7.74)	10.74 (10.76)
249	0.45[b]	98	111	$C_{16}H_{22}N_2O_2$			70.00 (70.03)	8.00 (8.08)	9.85 (10.21)
250	0.47[b]	92	117	$C_{18}H_{24}N_2O_2$			71.85 (71.96)	8.23 (8.05)	9.15 (9.32)
251	0.50[b]	90	55	$C_{21}H_{24}N_2O_2$	336.1838	336.1844	74.32 (74.97)	7.23 (7.19)	8.14 (8.32)

Tlc development solvent : [a] ether, [b] ether:ethanol (8:2 v/v).

Table 25. Ir[a,b] and ^{1}H nmr[c] spectral data for (2R,2S)-1-(isoquinol-5-yloxy) -2,3-epoxypropane (**247**) and (2R,2S)-1-(isoquinol-5-yloxy) -3-alkylamino-2-propanols (**248-251**).



247



248, R^2= $CH(CH_3)_2$; **249**, R^2= $C(CH_3)_3$;

250, R^2= Cyclohexyl; **251**, R^2= $(CH_2)_3$-Ph.

Compd.	ir (cm^{-1}) (OH) (NH)	^{1}H nmr δ (ppm)
247	1248 (oxirane C-O)[a]	2.86 (d, J_{vic}= 3.0 Hz of d, J_{gem}= 4.5 Hz, 1H, H_A); 3.01 (d, J_{vic}= 4.5 Hz of d, J_{gem}= 4.5 Hz, 1H, H_M); 3.51 (m, 1H, H_X); 4.14 (d, J_{vic}= 6.0 Hz of d, J_{gem}= 10.5 Hz, 1H, $H_{A'}$); 4.46 (d, J_{vic}= 3.0 Hz of d, J_{gem}= 10.5 Hz, 1H, $H_{M'}$); 7.02 (d, $J_{6,7}$= 7.5 Hz of d, $J_{6,8}$= 1.2 Hz, 1H, isoquinolyl H-6); 7.50 (d, $J_{6,7}$= 7.5 Hz of d,$J_{7,8}$= 7.5 Hz, 1H, isoquinolyl H-7); 7.6 (d, $J_{7,8}$= 7.5 Hz of d, $J_{6,8}$= 1.2 Hz, 1H, isoquinolyl H-8); 8.06 (d, $J_{3,4}$= 6.0 Hz, 1H, isoquinolyl H-4); 8.56 (d, $J_{3,4}$= 6.0 Hz, 1H, isoquinolyl H-3).9.23 (d, $J_{1,3}$= 0.75 Hz, 1H, isoquinolyl H-1).

Table 25. (cont.)

248	3352, 3244^b	1.12 [d, J= 6.0 Hz, 6H, -CH($\underline{CH}_3$)$_2$]; 2.86 (m, 2H; -$\underline{CH}$(CH_3)$_2$, -CH(OH)-C$\underline{H}$H^1-); 3.02 (d, J_{vic}= 4.0 Hz of d, J_{gem}= 12.0 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-); 3.84 (br s, 2H, NH, OH, exchange with deuterium oxide); 4.18 [m, 3H; -O-CH_2-$\underline{CH}$(OH)-, -O-$\underline{CH_2}$-CH(OH)-]; 7.04 (d, $J_{6,7}$= 7.5 Hz of d, $J_{6,8}$= 1.2 Hz, 1H, isoquinolyl H-6); 7.51 (d, $J_{6,7}$= 7.5 Hz of d, $J_{7,8}$= 7.5 Hz, 1H, isoquinolyl H-7); 7.56 (d, $J_{7,8}$= 7.5 Hz of d, $J_{6,8}$= 1.2 Hz, 1H, isoquinolyl H-8); 8.0 (d, $J_{3,4}$= 6.0 Hz isoquinolyl H-4); 8.53 (d, $J_{3,4}$= 6.0 Hz, 1H, isoquinolyl H-3); 9.22 (s, 1H, isoquinolyl H-1).
249	3377, 3254^b	1.15 (s, 9H, t-Bu); 2.79 (d, J_{vic}= 7.0 Hz of d, J_{gem}= 12.0 Hz, 1H, -CH(OH)-C$\underline{H}$H^1-NH-); 2.98 (d, J_{vic}= 4.0 Hz of d, J_{gem}= 12.0 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-); 4.0 (br s, 2H, N$\underline{H}$ and O$\underline{H}$, exchange with deuterium oxide); 4.11 [m, 1H, -O-CH_2-$\underline{CH}$(OH)-]; 4.19 [m, 2H, -O-$\underline{CH_2}$-CH(OH)-]; 7.03 (d, $J_{6,7}$= 7.5 Hz of d, $J_{6,8}$= 1.2 Hz, 1H, isoquinolyl H-6); 7.51 (d, $J_{6,7}$= 7.5 Hz of d, $J_{7,8}$= 7.5 Hz, 1H, isoquinolyl H-7); 7.56 (d, $J_{7,8}$= 7.5 Hz of d, $J_{6,8}$= 1.2 Hz, 1H, isoquinolyl H-8); 8.0 (d, $J_{3,4}$= 6.0 Hz isoquinolyl H-4); 8.53 (d, $J_{3,4}$= 6.0 Hz, 1H, isoquinolyl H-3); 9.22 (s, 1H,isoquinolyl H-1).
250	3082, 3238^b	1-2 (m, 10H, cyclohexyl H_2-H_6); 2.46 (m, 1H, cyclohexyl H_1); 2.84 (d, J_{vic}= 8.0 Hz of

Table 25. (cont.)

		d, J_{gem}= 12.0 Hz, 1H, -C$\underline{H}$H^1-NH-); 3.04 (d, J_{vic}= 4.0 Hz of d, J_{gem}= 12.0 Hz, 1H, -CH$\underline{H}^1$-NH-); 4.16 [m, 3H, -O-CH$_2$-$\underline{CH}$(OH)-, -O-$\underline{CH_2}$-CH(OH)-]; 7.02 (d, $J_{6,7}$= 7.5 Hz, 1H, isoquinolyl H-6); 7.5 (d, $J_{6,7}$= 7.5 Hz of d, $J_{7,8}$= 7.5 Hz, 1H, isoquinolyl H-7); 7.56 (d, $J_{7,8}$= 7.5 Hz, 1H, isoquinolyl H-8); 8.0 (d, $J_{3,4}$= 6.0 Hz isoquinolyl H-4); 8.52 (d, $J_{3,4}$= 6.0 Hz, 1H, isoquinolyl H-3); 9.21 (s, 1H, isoquinolyl , H-1).
251	3234^b	1.86 (quintet, J= 7Hz, 2H, -CH$_2$-$\underline{CH_2}$-CH$_2$-Ph); 2.71 (m, 4H, -NH-$\underline{CH_2}$-CH$_2$-$\underline{CH_2}$-Ph) 2.86 (d, J_{vic}= 8.0 Hz of d, J_{gem}= 12.0 Hz , 1H, CH(OH)-C$\underline{H}$H^1-NH-); 2.97 (d, J_{vic}= 4.0 Hz of d, J_{gem}= 12.0 Hz, 1H, -CH$\underline{H}^1$-NH-); 4.18 [m, 3H; -O-CH$_2$-$\underline{CH}$(OH)-, -O-$\underline{CH_2}$-CH(OH)-]; 7.02 (d, $J_{6,7}$= 7.5 Hz of d, $J_{6,8}$= 1.2 Hz, 1H, isoquinolyl H-6); 7.21 and 7.29 (two m, 5H, phenyl hydrogens); 7.50 (d, $J_{6,7}$= 7.5 Hz of d,$J_{7,8}$= 7.5 Hz, 1H, isoquinolyl H-7); 7.56 (d, $J_{7,8}$= 7.5 Hz of d, $J_{6,8}$= 1.20 Hz, 1H, isoquinolyl H-8); 7.98 (d, $J_{3,4}$= 6.0 Hz isoquinolyl H-4); 8.51 (d, $J_{3,4}$= 6.0 Hz, 1H, isoquinolyl H-3); 9.21 (s, 1H, isoquinolyl H-1). Note: The OH and NH resonances were not visible in the spectrum propably due to the fact that they are very broad.

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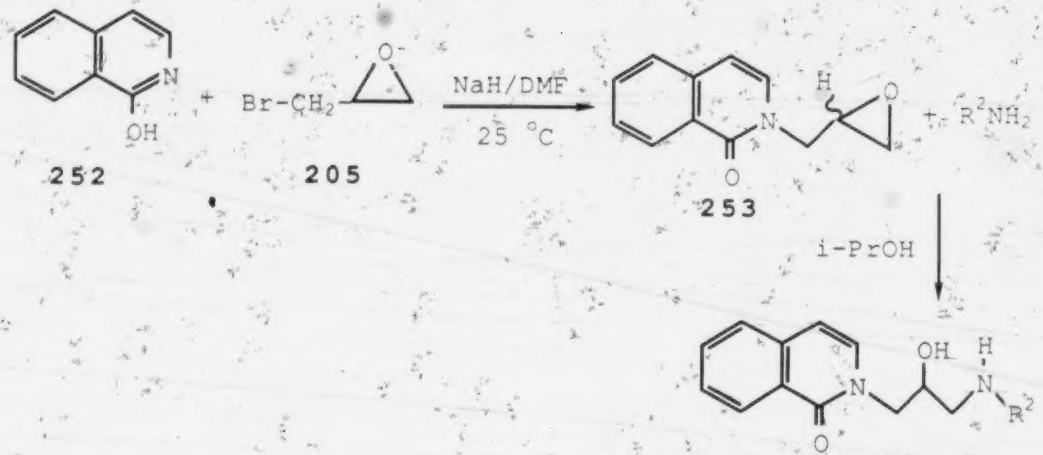
[a] Film. [b] KBr. [c] The spectrum was determined in $CDCl_3$

3.4.5.0.0 SYNTHESIS OF 1-[2-(ISOQUINOLIN-1-ONE)]-3-ALKYLAMINO -2-PROPANOLS.

The isocarbostyril moiety, commonly referred to as 1-hydroxyisoquinoline, is present in compounds that exhibited a combination of β-blocking and vasodilating activity such as **(83)**[345]. Cardiac stimulant activity was observed when a 2(1H)-quinolone[460] moiety was present. A number of class B adrenergic compounds have been reported, where the aryloxy moiety was replaced by a N-substituted-2-quinolinone, with N-substituents such as isopropyl, t-butyl or cyclohexylamino to determine the effect of these modifications upon β-adrenergic antagonist activity. A synthetic reaction similar to Procedure F described earlier in Scheme 11 was employed. Thus, reaction of 1-hydroxyisoquinoline **(252)** with **(205)** in DMF in the presence of NaH afforded the N-substituted product **(253)** which was purified by column chromatography to yield **(253)** as a white solid in 85% yield. The presence of the isomeric O-alkylation product was not observed by tlc or ^1H nmr. Further reaction of **(253)** with isopropyl, t-butyl or cyclohexylamine at 25 °C for 24-36 h provided the corresponding products **(254-256)** in 92-98% yield as outlined in Scheme 27. The physical data for **(253-256)** are presented in Table 26. The structures assigned to **(253-256)** in Scheme 27 were consistent with their ir and ^1H nmr spectral data which are summarized in Table 27.



254, R^2= $CH(CH_3)_2$; **255**, R^2= $C(CH_3)_3$;

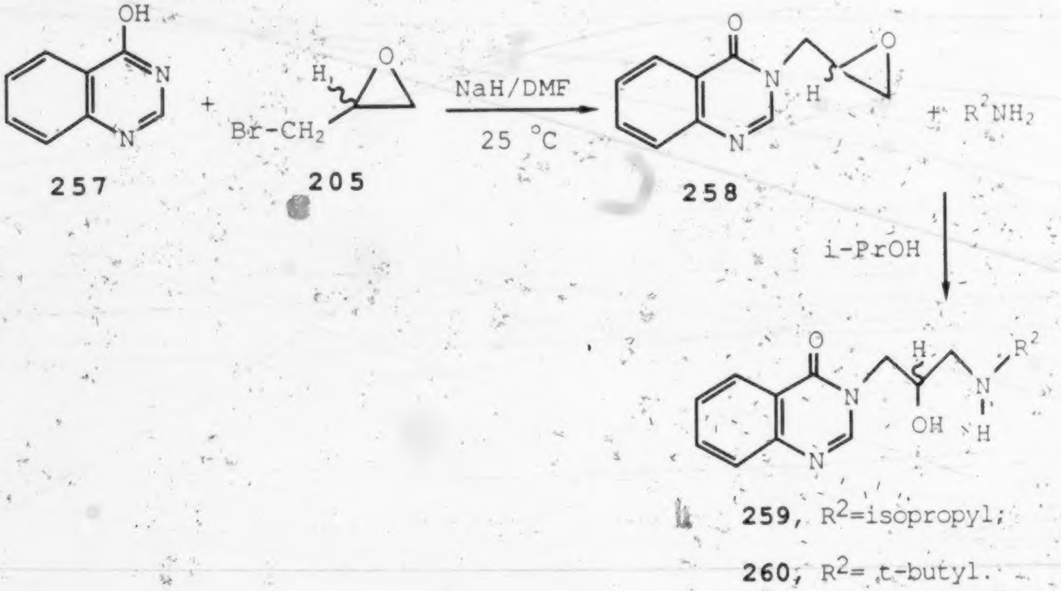
256, R^2= Cyclohexyl.

Scheme 27. Synthesis of 1-[2-(1-isoquinolonin-1-one)]-3-isopropyl (t-butyl, or cyclohexyl)amino-2-propanols (**254-256**).

3.4.6.0.0 SYNTHESIS OF 1-[3-(QUINAZOLIN-4-ONE)]-3-ALKYLAMINO -2-PROPANOLS.

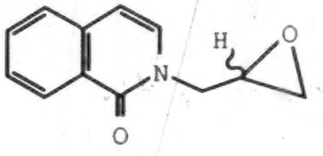
The introduction of a second annular nitrogen atom into the 3-position of a 4-hydroxyquinoline moiety was initiated to prepare class B aryloxypropanolamine analogues. It was of interest to determine the effect which a 3-(quinazolin-4-one) moiety, that can be envisaged as a 3-aza-4-hydroxyquinolyl group, has upon β-adrenergic antagonist activity. The reaction of 4-hydroxyquinazoline (**257**) with epibromohydrin (**205**) in DMF in the presence of NaH afforded exclusively the N-substituted product (**258**) in 78% yield. Reaction of (**258**) with isopropyl- or t-butylamine gave (**259-260**)in 98% yields as outlined in Scheme 28. The physical data for (**258-260**) are presented in Table 28.

The structures assigned to (**258-260**) are consistent with their ir and ^1H nmr spectral data which are summarized in Table 29. The ^1H nmr spectrum for (**258**) exhibited the typical AMX pattern described earlier for similar compounds in Figure 11. The ^1H nmr spectra for (**259-560**) showed that the methylene protons of the [O-CH_2-CH(OH)-] and [-CH(OH)-CH_2NH-] groups are chemically and magnetically non-equivalent. The ir spectra (cm^{-1}) showed a strong absorption for the C=O group of (**258-260**) at 1659-1679. A hydroxyl absorption band at 3407-3425 and a NH absorption band at 3265-3280 cm^{-1} for (**259-260**) were also present.

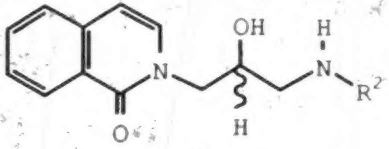

OH
N
N
257
+
H
O
Br-CH2
205
NaH/DMF
25 °C
O
N
H
O
N
258
+ R2NH2
i-PrOH
O
H
N
R2
N
OH
H
N
259, R2=isopropyl;
260, R2= t-butyl.

Scheme 28. Synthesis of (2R,2S)-1-[3-(quinazolin-4-one)]-3-isopropyl(or t-butyl)amino-2-propanol (**259-260**).

Table 26. Physical data for 1-[2-(1-isoquinolin-1-one)]-2,3-epoxypropane (**253**) and 1-[2-(1-isoquinolin-1-one)]-3-alkylamino-2-propanols (**254-256**).



253

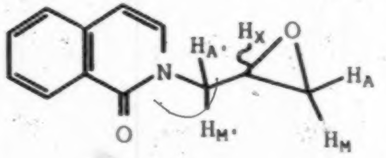


254, R^2= $CH(CH_3)_2$; **255**, R^2=$C(CH_3)_3$;
256, R^2= cyclohexyl.

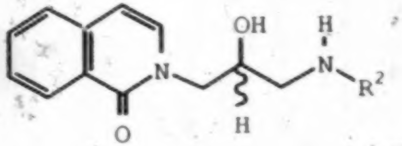
Compd.	Reaction time (h)	R_f	Yield, %	MP,°C	Formula	Microanalyses: Found (Calcd.) %C	%H	%N
253	12	0.51^a	85	82	$C_{12}H_{11}NO_2$	71.26	5.59	6.95
						(71.63)	(5.51)	(6.96)
254	20	0.48^b	98	56	$C_{15}H_{20}N_2O_2$	69.03	7.69	10.71
						(69.20)	(7.74)	(10.76)
255	30	0.49^b	98	94	$C_{16}H_{22}N_2O_2$	70.09	8.09	10.24
						(70.04)	(8.08)	(10.21)
256	36	0.50^b	92	134	$C_{18}H_{24}N_2O_2$	71.65	8.04	9.54
						(71.96)	(8.05)	(9.32)

Development solvent : ^{a} Ether, ^{b} Ether:ethanol (7:3 v/v)

Table 27. Ir[a] and ^1H nmr[b] spectral data for 1-[2-(1-isoquinolin-1-one)]-2,3-epoxypropane (**253**) and 1-[2-(1-isoquinolin-1-one)]-3-alkylamino-2-propanols (**254-256**).



253



254, R^2= $CH(CH_3)_2$; **255**, R^2= $CH(CH_3)_2$;
256, R^2= Cyclohexyl.

Compd.	ir (cm^{-1}) (OH)	ir (cm^{-1}) (C=O)	^1H nmr δ (ppm)
253		1657	2.59 (d, J_{vic}= 2.81 Hz of d, J_{gem}= 4.22 Hz, 1H, H_A); 2.86 (d, J_{vic}= 4.22 Hz of d, J_{gem}= 4.22 Hz, 1H, H_M); 3.36 (m, 1H, H_X); 3.81 (d, J_{vic}= 6.34 Hz of d, J_{gem}= 14.09 Hz, 1H, $H_{A'}$); 4.62 (d, J_{vic}= 2.81 Hz of d, J_{gem}= 14.09 Hz, 1H, $H_{M'}$); 6.50 (d, $J_{3,4}$= 7.0 Hz, 1H, isoquinolinone H-4); 7.12 (d, $J_{3,4}$= 7.0 Hz, 1H, isoquinolinone H-3); 7.50 (d, $J_{6,7}$= 5.8 Hz of d, $J_{7,8}$= 8.12 Hz of d, $J_{5,7}$= 1.16 Hz, 1H, isoquinolinonel H-7); 7.52 (d, $J_{5,6}$= 8.12 Hz, 1H, isoquinolinone H-5); 7.65 (d, $J_{5,6}$= 8.12 Hz of d, $J_{6,7}$= 5.80 Hz of d, $J_{6,8}$= 1.16 Hz, 1H, isoquinolinone H-6); 8.42 (d, $J_{7,8}$= 8.12 Hz of d, $J_{6,8}$= 1.16 Hz, 1H, isoquinolinone H-8).

Table 27. (cont.)

254	3327, 1649	1.02 and 1.03 [two d, J= 6.51 Hz, 3H each, -CH($\underline{CH}_3$)$_2$]; 2.53 (d, J_{vic}= 7.59 Hz of d, J_{gem}= 11.93 Hz, 1H, -CH(OH)-C$\underline{H}$H^1-NH-); 2.76 [m, 1H, -$\underline{CH}$(CH$_3$)$_2$]; 2.79 (d, J_{vic}= 4.30 Hz of d, J_{gem}= 11.93 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-); 3.88 (d, J_{vic}= 6.51 Hz of d, J_{gem}= 13.02 Hz, 1H, isoquinolone-C$\underline{H}$H^1-CH(OH)-]; 3.99 [m, 1H, -$\underline{CH}$(OH)-]; 4.31 (d, J_{vic}= 4.34 Hz of d, J_{gem}= 13.02 Hz, 1H, isoquinolone-CH$\underline{H}^1$-CH(OH)-); 6.50 (d, $J_{3,4}$= 7.5 Hz, 1H, isoquinolinone H-4); 7.22 (d, $J_{3,4}$= 7.5 Hz, 1H, isoquinolinone H-3); 7.48 (d, $J_{6,7}$= 6.87 Hz of d, $J_{7,8}$= 7.5 Hz of d, $J_{5,7}$= 1.25 Hz, 1H, isoquinolinone H-7); 7.52 (d, $J_{5,6}$= 7.5 Hz, 1H, isoquinolinone H-5); 7.64 (d, $J_{5,6}$= 7.5 Hz $J_{6,7}$= 6.87 Hz of d, $J_{6,8}$= 1.25 Hz, 1H, isoquinolinone H-6); 8.39 (d, $J_{7,8}$= 7.5 Hz of d, $J_{6,8}$= 1.25 Hz, 1H, isoquinolinone H-8).
255	3385, 1646	1.08 (s, 9H, t-Bu); 2.49 (d, $J_{vic.}$= 6.76 Hz of d, J_{gem}= 11.83 Hz, 1H, -CH(OH)-C$\underline{H}$H^1-NH-); 2.78 (d, J_{vic}= 5.07 Hz of d, J_{gem}= 11.83 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-); 3.83 (d, $J_{vic.}$= 7.6 Hz of d, J_{gem}= 12.67 Hz, 1H, isoquinolinone-C$\underline{H}$H^1-CH(OH)-]; 3.91 [m, 1H, -CH$_2$-$\underline{CH}$(OH)-]; 4.37 [d, J_{vic}= 3.38 Hz of d, J_{gem}= 12.67 Hz, 1H of isoquinolinone-CH$\underline{H}^1$-CH(OH)-]; 6.51 (d, $J_{3,4}$= 7.68 Hz, 1H, isoquinolinone H-4); 7.24 (d, $J_{3,4}$= 7.68 Hz, 1H, isoquinolinone H-3); 7.49 (d, $J_{6,7}$= 7.04 Hz of d, $J_{7,8}$=

Table 27. (cont.)

		7.68 Hz of d, $J_{5,7}$= 1.28 Hz, 1H, isoquinolinone H-7); 7.53 (d, $J_{5,6}$= 7.68 Hz of d, $J_{5,7}$= 1.28 Hz, 1H, isoquinolinone H-5); 7.65 (d, $J_{5,6}$= 7.68 Hz of d, $J_{6,7}$= 7.04 Hz of d, $J_{6,8}$= 1.28 Hz, 1H, isoquinolinone H-6); 8.42 (d, $J_{7,8}$= 7.68 Hz of d, $J_{6,8}$= 1.28 Hz, 1H, isoquinolinone H-8).
256	3180, 1648	0.81-1.89 (m, 10H, cyclohexyl H_2-H_6 hydrogens), 2.38 (m, 1H, cyclohexyl H_1); 2.54 (d, J_{vic}= 7.28 Hz of d, J_{gem}= 12.48 Hz, 1H, CH(OH)-C$\underline{H}$$H^1$-NH-); 2.85 (d, J_{vic}= 4.16 Hz of d, J_{gem}= 12.48 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-); 3.85 (d, J_{vic}= 8.32 Hz of d, J_{gem}= 12.48 Hz, 1H, isoquinolinone-C$\underline{H}$$H^1$-CH(OH)-]; 3.95 [m, 1H, -CH_2-$\underline{CH}$(OH)-]; 4.33 [d, J_{vic}= 4.18 Hz of d, J_{gem}= 12.48 Hz, 1H, isoquinolinone-CH$\underline{H}^1$-CH(OH)-]; 6.51 (d, $J_{3,4}$= 7.48 Hz, 1H, isoquinolinone H-4); 7.23 (d, $J_{3,4}$= 7.48 Hz, 1H, isoquinolinone H-3); 7.49 (d, $J_{6,7}$= 7.48 Hz of d, $J_{7,8}$= 8.84 Hz of d, $J_{5,7}$= 1.36 Hz, 1H, isoquinolinone H-7); 7.52 (d, $J_{5,6}$= 8.16 Hz of d, $J_{5,7}$= 1.36 Hz, 1H, isoquinolinone H-5); 7.64 (d, $J_{5,6}$= 8.16 Hz $J_{6,7}$= 7.48 Hz of d, $J_{6,8}$= 1.36 Hz, 1H, isoquinolinone H-6); 8.41 (d, $J_{7,8}$= 8.84 Hz of d, $J_{6,8}$= 1.36 Hz, 1H, isoquinolinone H-8).

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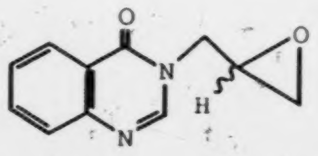
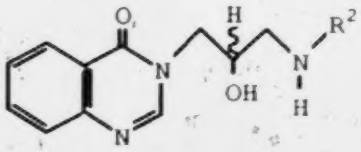
[a]KBr. [b]The spectrum was determined in $CDCl_3$

Table 28. Physical data for 1-[3-(quinazolin-4-one)]-2,3-epoxypropane (**258**) and 1-[3-(quinazolin-4-one)]-3-alkylamino-2-propanols (**259-260**).



258

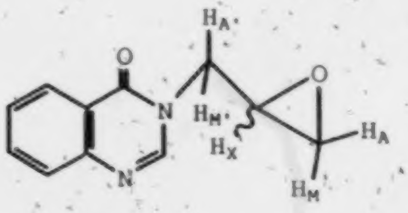


259, $R^2 = CH(CH_3)_2$; **260**, $R^2 = C(CH_3)_3$.

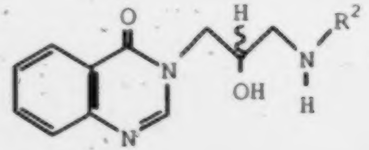
Compd.	Reaction time (hr)	R_f	Yield, %	MP,°C	Formula	Microanalyses: Found (Calcd.) %C	%H	%N
258	12	0.47^a, 0.7^b	78	86	$C_{11}H_{10}N_2O_2$	65.02 (65.33)	5.03 (4.98)	13.81 (13.85)
259	18	0.26^b	98	98	$C_{14}H_{19}N_3O_2$	64.21 (64.31)	7.39 (7.32)	16.04 (16.07)
260	24	0.30^b	98	103	$C_{15}H_{21}N_3O_2$	65.28 (65.43)	7.71 (7.68)	15.11 (15.26)

Tlc development solvent : ^{a} ether, ^{b} ether:ethanol (7:3 v/v).

Table 29. Ir[a] and ^{1}H nmr[b] spectral data for 1-[3-(quinazolin-4-one)]-2,3-epoxypropane (**258**) and 1-[3-(quinazolin-4-one)]-3-alkylamino-2-propanols (**259-260**).



258



259, R^2= $CH(CH_3)_2$; **260**, R^2= $C(CH_3)_3$.

Compd.	ir (cm^{-1}) (OH), (NH), (C=O)	^{1}H nmr δ (ppm)
258	1679	2.62 (d, J_{vic}= 3.33 Hz of d, J_{gem}= 4.44 Hz, 1H, H_A); 2.91 (d, J_{vic}= 4.44 Hz of d, J_{gem}= 4.44 Hz, 1H, H_M); 3.40 (m, 1H, H_X); 3.88 (d, J_{vic}= 5.55 Hz of d, J_{gem}= 15.21 Hz, 1H, $H_{A'}$) and 4.60 (d, J_{vic}= 3.33 Hz of d, J_{gem}= 15.21 Hz, 1H, $H_{M'}$); 7.56 ($J_{5,6}$= 8.47 Hz of d, $J_{6,7}$= 6.65 Hz of d, $J_{6,8}$= 1.21 Hz, 1H, quinazolinone H-6); 7.76 (d, $J_{7,8}$= 7.86 Hz of d, $J_{6,8}$= 1.21 Hz, 1H, quinazolinone H-8); 7.81 (d, $J_{6,7}$= 6.65 Hz of d, $J_{7,8}$= 7.86 Hz of d, $J_{5,7}$= 1.21 Hz, 1H, quinazolinone H-7); 8.09 (s, 1H, quinazolin-one H-2); 8.34 (d, $J_{5,6}$= 8.47 Hz of d, $J_{5,7}$= 1.21 Hz, 1H, quinazolinone H-5).

Table 29. (cont.)

259	3407, 3280, 1659	1.04 [two d, J= 6.37 Hz, 3H each, $-CH(\underline{CH}_3)_2$]; 2.53 (d, J_{vic}= 8.19 Hz of d, J_{gem}= 10.92 Hz, $-CH(OH)-C\underline{H}H^1-NH-$); 2.75 [m, 1H, $-\underline{CH}(CH_3)_2$]; 2.83 (d, J_{vic}= 3.64 Hz of d, J_{gem}= 10.92 Hz, 1H, $-CH(OH)-CH\underline{H}^1-NH-$); 3.75 (d, J_{vic}= 8.19 Hz of d, J_{gem}= 13.65 Hz, 1H, quinazolinone-$C\underline{H}H^1-CH(OH)-$]; 4.04 [m, 1H, $-\underline{CH}(OH)-$]; 4.33 (d, J_{vic}= 3.64 Hz of d, J_{gem} = 13.65 Hz, 1H, quinazolinone-$CH\underline{H}^1-CH(OH)-$]; 7.47 ($J_{5,6}$= 7.95 Hz of d, $J_{6,7}$= 7.95 Hz of d, $J_{6,8}$= 1.42 Hz, 1H, quinazolinone H-6); 7.66 (d, $J_{7,8}$= 7.38 Hz of d, $J_{6,8}$= 1.42 Hz, 1H, quinazolinone H-8); 7.74 (d, $J_{6,7}$= 7.95 Hz of d, $J_{7,8}$= 7.38 Hz of d, $J_{5,7}$= 1.42 Hz, 1H, quinazolinone H-7); 8.20 (s, 1H, quinazolinone H-2); 8.22 (d, $J_{5,6}$= 7.95 Hz of d, $J_{5,7}$= 1.42 Hz, 1H, quinazolinone H-5).
260	3425, 3265, 1664	1.09 (s, 9H, t-Bu); 2.49 (d, J_{vic}= 8.4 Hz of d, J_{gem}= 12.6 Hz, 1H, $-CH(OH)-C\underline{H}H^1-NH-$); 2.83 (d, J_{vic}= 4.2 Hz of d, J_{gem}= 12.6 Hz, 1H, $-CH(OH)-CH\underline{H}^1-NH-$); 3.77 (d, J_{vic}= 8.4 Hz of d, J_{gem}= 13.65 Hz, 1H, quinazolinone-$C\underline{H}H^1-CH(OH)-$]; 3.95 [m, 1H, $-CH_2-\underline{CH}(OH)-$]; 4.38 [d, J_{vic}= 3.45 Hz of d, J_{gem}= 13.65 Hz, 1H, quinazolinone-$CH\underline{H}^1-CH(OH)-$]; 7.51 ($J_{5,6}$= 8.16 Hz of d, $J_{6,7}$= 6.81 Hz of d, $J_{6,8}$= 1.36 Hz, 1H, quinazolinone H-6); 7.72 (d, $J_{7,8}$= 8.16 Hz of d, $J_{6,8}$= 1.36 Hz, 1H, quinazolinone H-

Table 29. (cont.)

8); 7.78 (d, $J_{6,7}$= 6.81 Hz of d, $J_{7,8}$= 8.16 Hz of d, $J_{5,7}$= 1.36 Hz, 1H, quinazolinone H-7); 8.22 (s, 1H, quinazolinone H-2); 8.28 (d, $J_{5,6}$= 8.16 Hz of d, $J_{5,7}$= 1.36 Hz, 1H, quinazolinone H-5).

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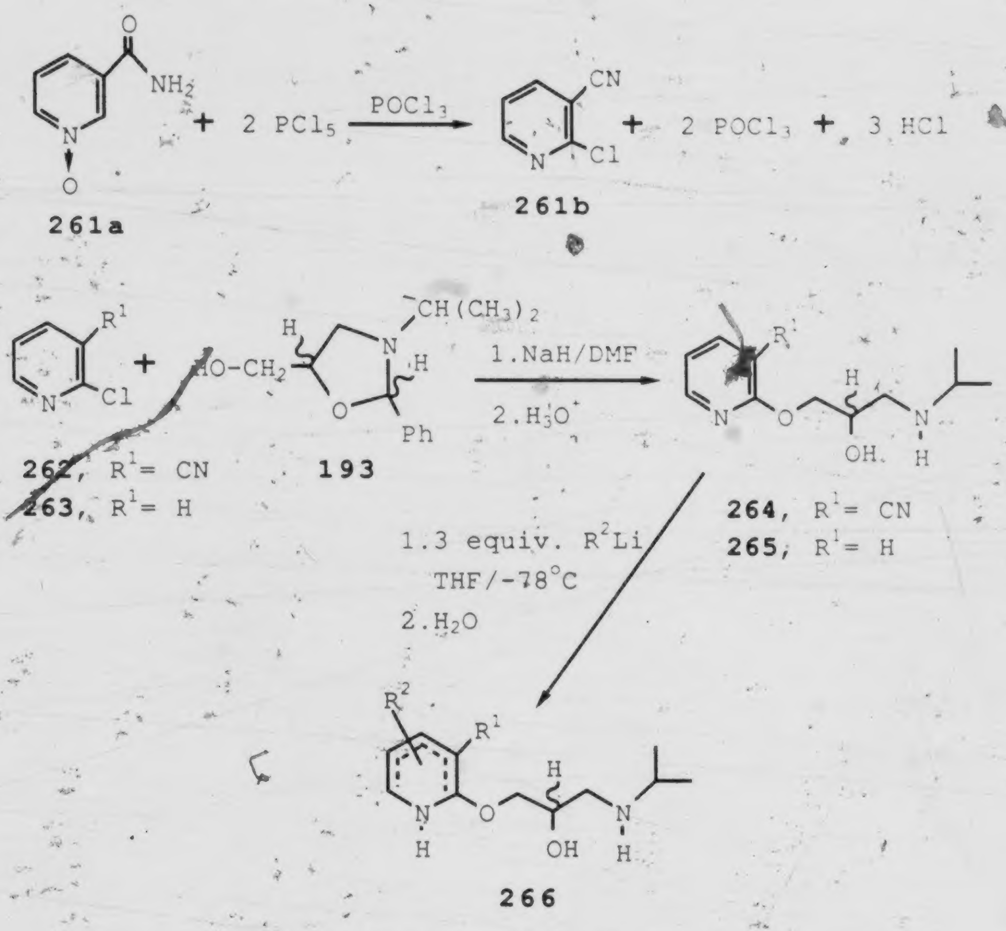
[a] KBr .

[b] The spectrum was determined in $CDCl_3$

3.5.0.0.0 ATTEMPTED SYNTHESIS OF 1-{2-[4-(or 6)-SUBSTITUTED-1,4-(or 1,6-)DIHYDROPYRIDYLOXY]}-3-ISOPROPYLAMINO-2-PROPANOL (266).

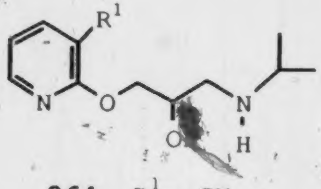
The general procedure for the synthesis of 1-(3-cyano-2-pyridyloxy)-3-isopropylamino-2-propanol (**264**) and the corresponding analogue (**265**)[382,452] are outlined in Scheme 29. The physical data for (**264-265**) are presented in Table 30. The structures assigned to (**264-265**) are consistent with their ir and ^{1}H nmr spectral data which are summarized in Table 31. The 3-cyano substituent present in (**264**) is a significant determinant of antihypertensive and vasodilating activity. Replacement of the cyano substituent present in (**264**) by a hydrogen substituent provides (**265**) which possesses antihypertensive activity but is essentially devoid of any vasodilating effect[382]. These results stimulated us to investigate the effect which reduction of the pyridine ring of (**264-265**) to a dihydropyridine ring had upon activity. Thus, reaction of (**264**) or (**265**) with either phenyl- or methyl lithium in THF at -78 °C did not occur to yield the target 1,4- or 1,6-dihydropyridyl analogues (**266**) since starting material was recovered. When the reaction was carried out at 25 °C, the reaction mixture was comprised of many compounds without any major product as indicated by tlc, from which 1,4- or 1,6-dihydropyridyl products (**266**) could not be isolated by silica gel G tlc.


NH2
+ 2 PCl5
POCl3
CN
Cl
+ 2 POCl3 + 3 HCl
261a
261b
R1
Cl
+
HO-CH2
CH(CH3)2
H
Ph
1.NaH/DMF
2.H3O+
262, R1= CN
263, R1= H
193
OH
264, R1= CN
265, R1= H
1.3 equiv. R2Li
THF/-78°C
2.H2O
R2
266

R^1= CN, H; R^2= Ph, Me.

Scheme 29. Synthetic procedure for the attempted synthesis of 1,4- or 1,6-dihydropyridyl analogues (**266**) of 1-(2-pyridyloxy)-3-isopropylamino-2-propanols (**264-265**).

Table 30. Physical data for 1-[2-(3-cyano)pyridyloxy]-3-isopropylamino-2-propanol (**264**) and 1-[2-pyridyloxy]-3-isopropylamino-2-propanol (**265**).

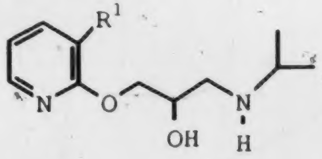


264, R^1 = CN
265, R^1 = H

Compd.	R^1	$R_f{}^a$	Yield, %	MP,°C	Formula	Microanalyses: Found (Calcd.) %C	 %H	 %N
264	CN	0.50	75	113-114	$C_{12}H_{17}N_3O_2$	60.76 (61.25)	7.21 (7.28)	17.40 (17.85)
265	H	0.48	70	oil	$C_{11}H_{18}N_2O$[illegible]	62.79 (62.85)	8.68 (8.57)	13.18 (13.33)

[a] Silica gel tlc using ether:ethanol (7:3 v/v) as development solvent.

Table 31. Ir[a,b] and ^{1}H nmr[c,d] spectral data for 2-[3-(isopropylamino)-3-substituted (or unsubstituted)pyridines.



264, R^1= CN

265, R^1= H

Compd.	ir (cm^{-1})	^{1}H nmr δ (ppm)
264[c]	3350 (OH), 2229 (CN)[b]	1.12 (d, J= 6.8 Hz, 6H, $-CH(\underline{CH}_3)_2$]; 2.49 (br s, 2H, OH, NH, exchange with deuterium oxide); 2.79 [m, 1H, $-\underline{CH}(CH_3)_2$]; 2.83 (d, J_{vic}= 7.7 Hz of d, J_{gem}= 11.5 Hz, -CH(OH)-C$\underline{H}$H^1-NH-); 2.89 (d, J_{vic}= 3.8 Hz of d, J_{gem}= 111.5 Hz, 1H, -CH(OH)-CH$\underline{H}^1$-NH-); 4.08 [m, 1H, -$\underline{CH}$(OH)-]; 4.45 (d, J_{vic}= 5.7 Hz of d, J_{gem}= 11.55 Hz, 1H, O-C$\underline{H}$H^1-CH(OH)-]; 4.8 (d, J_{vic}= 4.8 Hz of d, J_{gem} = 11.5 Hz, 1H, O-CH$\underline{H}^1$-CH(OH)-]; 7.04 (d, $J_{4,5}$= 6.7 Hz of d, $J_{5,6}$= 5.3 Hz of d, 1H, pyridyl H-5); 7.94 (d, $J_{4,5}$= 6.7 Hz of d, $J_{4,6}$= 2.4 Hz, 1H, pyridyl H-4); 8.37 (of d, $J_{5,6}$= 5.3 Hz of d, $J_{4,6}$= 2.4 Hz, 1H, pyridyl H-6).

Table 31. (cont.)

265^d	3295 (OH)^a	1.06 (d, J= 7 Hz, 6H, $-CH(\underline{CH}_3)_2$]; 2.56 (d, J_{vic}= 8.3 Hz of d, J_{gem}= 11.4 Hz, $-CH(OH)-C\underline{H}H^1-NH-$); 2.75 (d, J_{vic}= 3.1 Hz of d, J_{gem}= 11.4 Hz, 1H, $-CH(OH)-CH\underline{H}^1-NH-$); 2.77 [h, J= 7 Hz, 1H, $-\underline{CH}(CH_3)_2$]; 3.36 (br s, 2H, OH, NH, exchange with deuterium oxide); 3.96 [m, 1H, $-\underline{CH}(OH)-$]; 4.26 (m, 2H, $O-CH_2-CH(OH)-$]; 6.7 (d, $J_{3,4}$= 10.0 Hz, 1H, pyridyl H-3); 6.79 (d, $J_{4,5}$= 8.7 Hz of d, $J_{5,6}$= 6.7 Hz of d, 1H, pyridyl H-5); 7.51 (d, $J_{3,4}$= 10.0 Hz of d, $J_{4,5}$= 8.7 Hz of d, $J_{4,6}$= 2.0 Hz, 1H, pyridyl H-4); 8.07 (of d, $J_{5,6}$= 6.7 Hz of d, $J_{4,6}$= 2.0 Hz, 1H, pyridyl H-6).

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^{a}Film , ^{b}KBr .

The spectrum was determined in ^{c}$CDCl_3$ or ^{d}CCl_4.

4.0.0.0.0 TISSUE PREPARATION AND DETERMINATION OF ID_{50} AND pA_2 VALUES.

4.1.0.0.0 β_1-ADRENERGIC ANTAGONIST TEST PROCEDURE.

White male guinea-pigs (GP) between 400-600 g in weight were killed by a sharp blow to the head, bled and then decapitated. The chest wall was opened and the right and left atria were carefully dissected, freed from adhesive tissue and mounted in separate jacketed water baths containing Hepes buffered physiological saline solution (HPSS) at 37 °C that was aerated with O_2. The HPSS had the following composition (mM/L): NaCl 135.0, $CaCl_2$ 2.2, KCl 5.6, $MgCl_2$ 2.1, glucose 10.0, Hepes-NaOH (pH 7.4) 10.0. Contractions were recorded isotonically with a preload resting tension of 0.75 g. The isolated left atrium was electrically stimulated at a constant rate by square pulses of 1.5 msec duration and an intensity approximately twice that of threshold (2.0 volts). The pulses were delivered by an electronic stimulator (Grass S44) through an isolation unit (Grass SIU5) at a stimulation rate of 2 Hz, which corresponded to 85-95 per cent of the maximal activity. After an equilibration period of 45 to 60 minutes, cumulative dose response curves were obtained for the β-agonist isoproterenol (INA) using the method described by D. Horii.[461] Doses of the INA were added cumulatively to the spontaneously beating right and electrically stimulated left atria in a geometrical fashion in steps of one half log 10 molar doses. The next dose was not added until the response to the previous dose had reached a plateau. The total volume of solution added to the tissue bath during the experiment did not exceed more than 4% of the total bath volume. Cumulative dose-response curves were obtained to the β-agonist isoproterenol (INA) for the β_1-receptor (heart) for the

β_2-receptor (trachea). The maximal dose for isoproterenol (INA) and carbachol were determined from the dose response curves as shown in Fig. 13 (a, b or c).

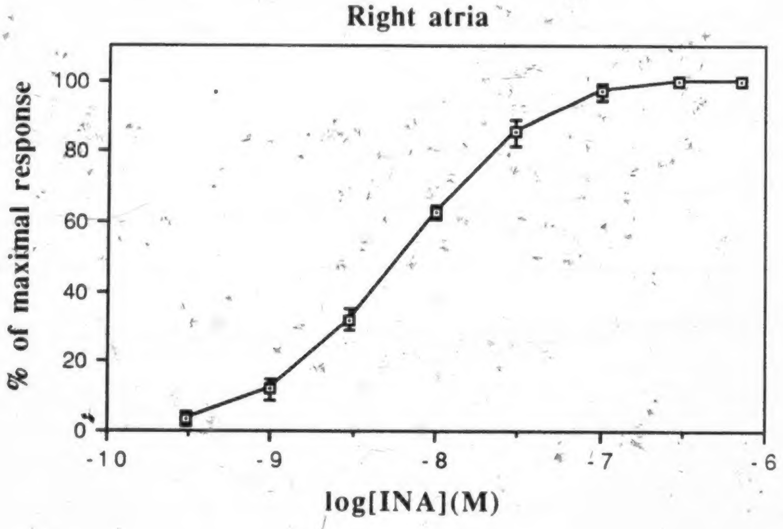


Fig. 13a. The dose response curve for determination of the maximal dose for isoproterenol (INA) on right atrium. Each point represents the mean of 30 experiments ± SEM.

From the dose response curves (Fig. 13a, b, c), the maximal dose required to produce an effect was determined for each agonist. The maximal doses were 3 x 10^{-7} M/L for INA on atria and 1 x 10^{-5} M/L for carbacol on trachea. The maximal dose was chosen as the control dose for subsequent experiments where the ID_{50} of the test drug (antagonist) was evaluated for the determination of negative inotropic and chronotropic effects.

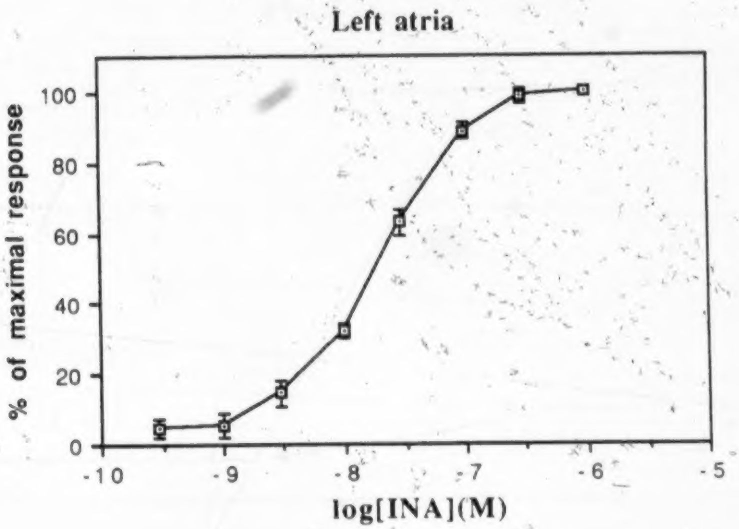


Fig. 13b. The dose response curve for determination of the maximal dose for isoproterenol (INA) on left atrium. Each point represents the mean of 30 experiments ± SEM.

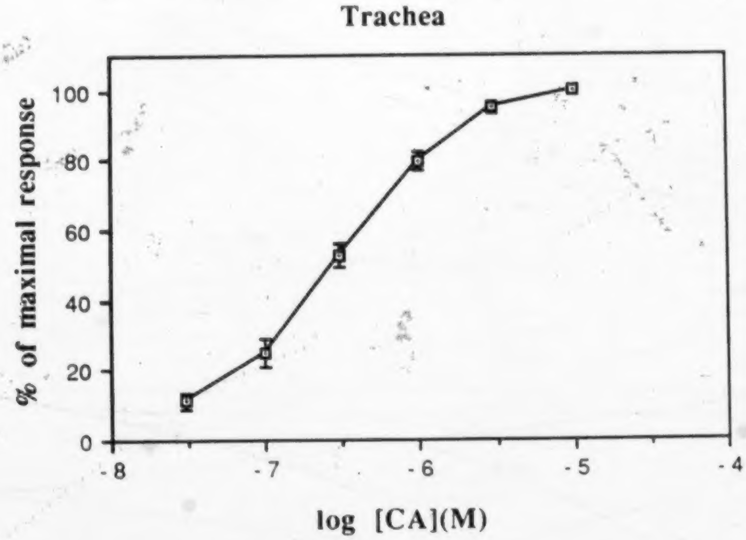


Fig. 13c. The dose response curve for determination of the maximal dose for carbachol (CA) on trachea. Each point represents the mean of 40 experiments ± SEM.

The ID_{50} value [+/- SEM (standard error of the mean)] is defined as the concentration of the antagonist that inhibits the control response by 50% of the starting inotropic contractility or chronotropic rate of the atrium (Fig. 14). A minimum of three determinations were acquired and the ID_{50} value was determined graphically or by linear regression analysis of three points on the linear portion (20 to 80% inhibition) of the dose-response curve of the antagonist. A minimum of three tissues were used for each test compound. The relative potency order for the antagonists was determined by comparison of the test drug ID_{50} with the ID_{50} of the standard antagonist (propranolol or metoprolol) which was determined by the same procedure as the test compounds.

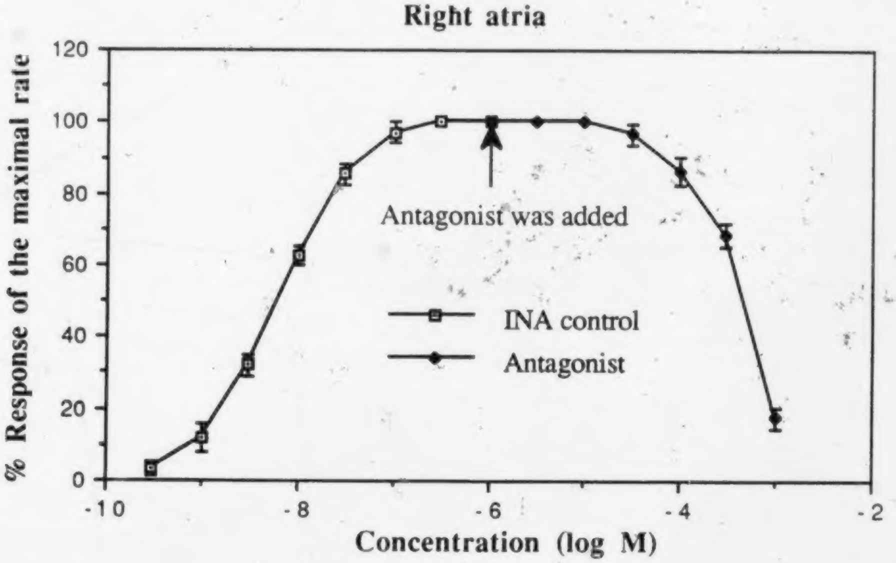
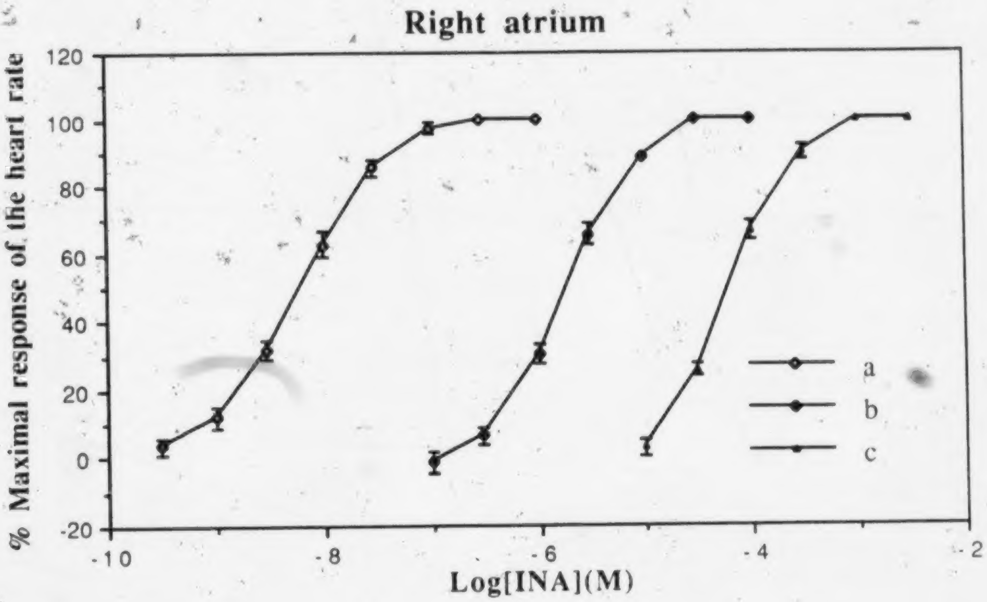


Fig.14. Dose-respose curve for the determination of the ID_{50} value for the chronotropic effect of the antagonist (**255**). Each point represents the mean of 3 experiments ± SEM.

Consequently, the right and left atria were incubated with the β-blocker at two different doses chosen as a factor of ten in the ID_{35} to ID_{70} range for 30 minutes, and the cumulative dose-response curve for INA was again established in the presence of β-blocker as illustrated in Fig. 15.



a= Dose-response control curve for INA

b= Dose-response curve for INA in the presence of 3×10^{-6} M of (**212**)

c= Dose-response curve for INA in the presence of 3×10^{-5} M of (**212**)

Fig. 15. Dose-response curves for the determination of pA_2 value for the antagonist (**212**). Each point represents the mean of 3 experiments ± SEM.

The dose-response curve was shifted to the right when the concentration of antagonist was increased by a factor of ten, as illustrated in Fig. 15. Two ID_{50} values were determined for dose-response curves (b or c) and pA_2 values were calculated according to the method of Schild[462] which is a graph of log (X-1) plotted against the molar concentration of the antagonist. To find log (X-1), where X is the dose ratio (DR), which is the ratio of the dose of isoproterenol (isoprenaline) (INA) (ID_{50} of curve b) acting in the presence of the antagonist divided by the dose of isoproterenol (ID_{50} of curve a) acting alone, that both produce the same percentage increase in heart rate; for example X= b/a or c/a (ID_{50} of curve b or c divided by the ID_{50} of curve a). The X value in equation (X-1) was replaced by b/a or c/a to give (b/a -1) or log(X-1) = log(b/a -1) in Fig. 15. The pA_2 value was determined graphically or by linear regression analysis by plotting the log(X-1) value against the molar concentration of the antagonist present. The pA_2 value which is read from the graph, is the point where the line crosses the X axis (Fig. 16).

4.2.0.0.0 β_2-ADRENERGIC ANTAGONIST TEST PROCEDURE.

The trachea from a guinea-pig was removed by dissection, transferred to a dish containing HPSS solution and cut transversely between the segments of cartilage to obtain a number of rings of tracheal muscle. These rings were freed of all fat tissue and blood vessel with extreme care to avoid stretching the ring. Several rings, usually 6, were sutured together, side by side, using polyester thread to form a chain, which was then mounted vertically in a HPSS solution

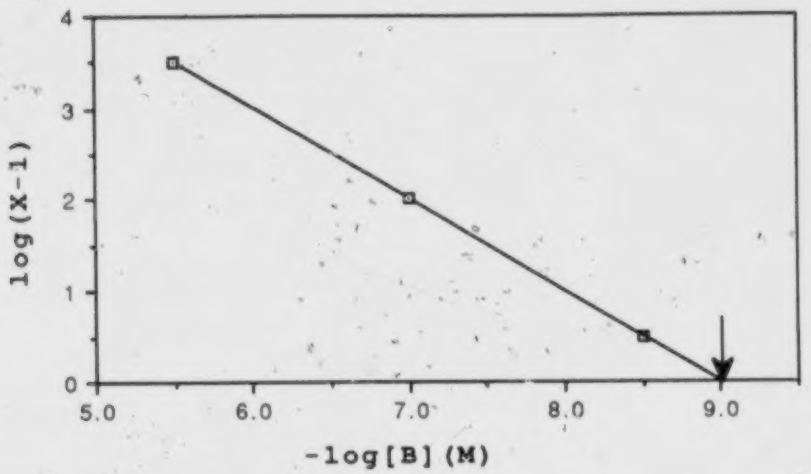


Fig. 16. A typical plot for the calculation of the pA_2 value. [B] is the concentration of antagonist. The arrow indicates the pA_2 value.

water-jacketed bath (10 mL) at 37 °C that was aerated with O_2 as illustrated in Fig. 17. An initial basal tension of 0.25 g was applied to each tracheal chain and the tisuue was allowed to stand for 1 h prior to use. A constant level of tone was induced by the administration of carbachol to achieve the maximum response. Following this, and without washing, a cumulative dose-response curve to the antagonist was determined to calculate the ID_{50}. Cumulative dose-response curves to isoproterenol were determined before and after treatment with the antagonists cited above. Two concentrations of each antagonist were used for each tracheal ring chain where the difference between the two concentrations was a factor of ten. The pA_2 values were calculated using the method of Schild[462] described previously.

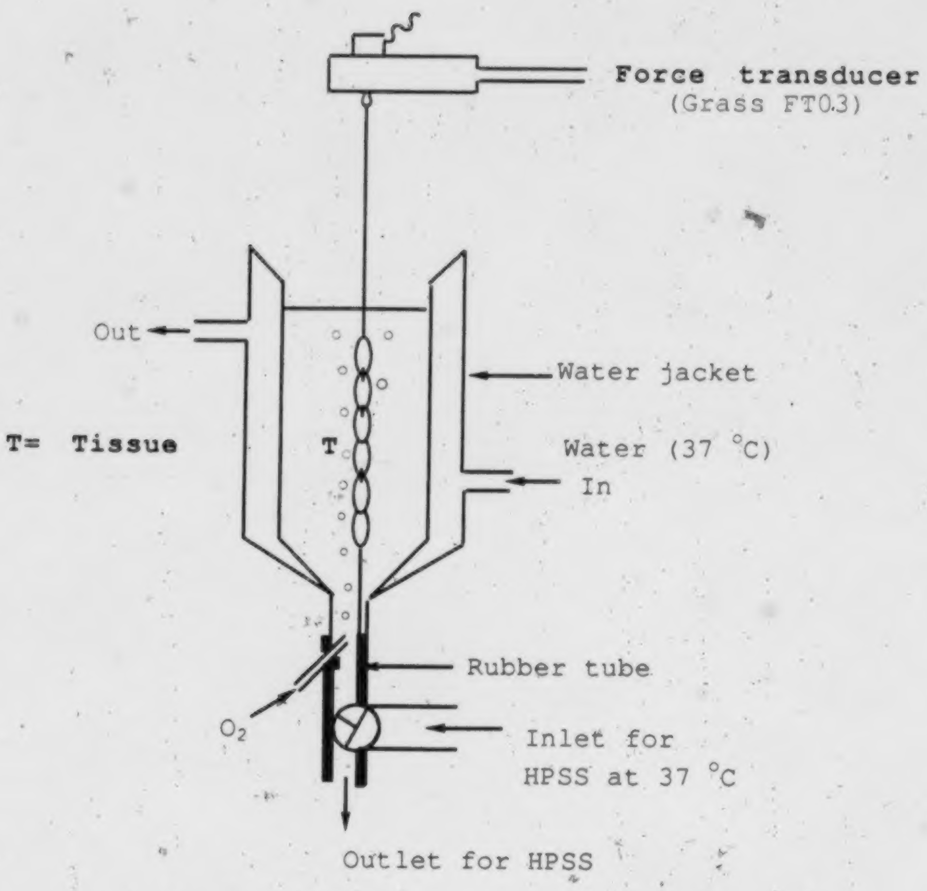

Force transducer
(Grass FT0.3)
Out
Water jacket
T= Tissue
T
Water (37 °C)
In
Rubber tube
O_2
Inlet for
HPSS at 37 °C
Outlet for HPSS

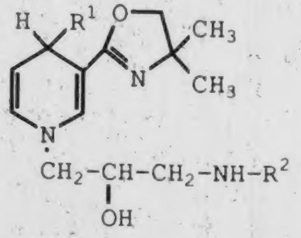
Fig. 17. Schematic representation of the guinea-pig trachea chain set up

4.3.0.0.0 PHARMACOLOGICAL RESULTS AND DISCUSSIONS.

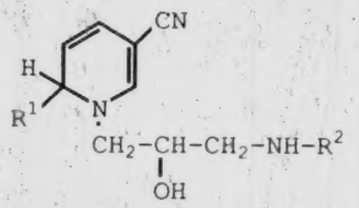
4.3.1.0.0 PHARMACOLOGICAL EVALUATION OF 1-{1-[2-,4- or 6-ALKYL(PHENYL)-3-(CYANO or 4,4-DIMETHYLOXAZOLIN-2-YL)]DIHYDROPYRIDYL}-3-ALKYLAMINO-2-PROPANOLS, 1-(2-ISOQUINOLIN-1-ONE)-3-ALKYLAMINO-2-PROPANOLS and 1-(3-QUINAZOLIN-4-ONE)-3-ALKYLAMINO-2-PROPANOLS.

A number of selected compounds from the 1-{1-[2-,4- or 6-alkyl(phenyl)-3-(cyano or 4,4-dimethyloxazolin-2-yl)]-1,2-(1,4- or 1,6-)dihydropyridyl}-3-alkylamino-2-propanol series of compounds were tested *in vitro* to determine the effect which a dihydropyridyl ring system and the absence of an ethereal atom had upon β-adrenergic antagonist activity. The pharmacological test procedures are described in section 4.0.0.0.0. The ID_{50} values for selected compounds are presented in Table 32. The test results indicated that replacement of the aryloxy moiety of propranolol by a 1,2-; 1,4- or 1,6-dihydropyridine ring system resulted in a marked decrease in pharmacological activity that was non-selective for β_1 and β_2-adrenergic receptors. β_1/β_2 Activity was reduced approximately 100 fold relative to the reference drugs metoprolol or propranolol. Although (**159**) is about three times more potent than (**148**) and (**156**), this observation is based on only one compound in each group and the differences are small. Thus, the isomeric 1,2-; 1,4-; or 1,6-dihydropyridyl rings present in compounds (**148, 156 and 159**) confer similar potencies. Compound (**161**), which posesses two chiral centers, exists as a mixture of four diastereomers (SS, RR, SR and RS). These diastereomers could in theory possess different β-adrenergic antagonist activites.

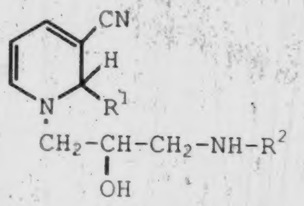
Table 32. ID_{50} values for β-Adrenergic antagonist activity of 1-{1-[2-,4- or 6-alkyl(phenyl)-3-(cyano or 4,4-dimethyloxazolin-2-yl)]-1,2-, 1,4- or 1,6-dihydropyridyl}-3-alkylamino-2-propanols.



148, 149



156, 157, 161, 164



159, 166

Compd.	R^1	R^2	Right atria (chronotropic effect) $^aID_{50}$ ± SEM (β_1)	Left atria (inotropic effect) $^aID_{50}$ ± SEM	Trachea (smooth muscle) $^aID_{50}$ ± SEM (β_2)	Selectivity ^{b}Ratio β_1/β_2
148	n-Bu	$CH(CH_3)_2$	$1.94 \times 10^{-4} \pm 0.93$ (6)^c	$1.90 \times 10^{-4} \pm 0.83$ (4)	$2.04 \times 10^{-4} \pm 0.89$ (8)	0.95
149	n-Bu	$C(CH_3)_3$	$1.86 \times 10^{-4} \pm 0.93$ (6)	$1.94 \times 10^{-4} \pm 0.87$ (5)	$6.16 \times 10^{-5} \pm 0.97$ (8)	3.01
156	n-Bu	$CH(CH_3)_2$	$1.99 \times 10^{-4} \pm 0.60$ (3)	T^d	$1.65 \times 10^{-4} \pm 0.93$ (6)	1.20
157	n-Bu	$C(CH_3)_3$	$1.38 \times 10^{-4} \pm 0.77$ (3)	$3.01 \times 10^{-4} \pm 0.91$ (3)	$1.90 \times 10^{-4} \pm 0.87$ (12)	0.72
159	n-Bu	$CH(CH_3)_2$	$7.41 \times 10^{-5} \pm 0.85$ (6)	$2.39 \times 10^{-4} \pm 0.79$ (6)	$9.54 \times 10^{-5} \pm 0.95$ (6)	0.77
161	t-Bu	$CH(CH_3)_2$	$3.09 \times 10^{-4} \pm 0.89$ (4)	$4.80 \times 10^{-3} \pm 0.31$ (3)	$3.31 \times 10^{-4} \pm 0.83$ (10)	0.92

Table 32. (cont.)

Compd.	R^1	R^2	Right atria (chronotropic effect) $^{a}ID_{50}$ ± SEM (β_1)	Left atria (inotropic effect) $^{a}ID_{50}$ ± SEM	Trachea (smooth muscle) $^{a}ID_{50}$ ± SEM (β_2)	Selectivity ^{b}Ratio β_1/β_2
164	t-Bu	$CH(CH_3)_2$	$2.95 \times 10^{-4} \pm 0.85$ (10)^{c}	T^{d}	$1.18 \times 10^{-4} \pm 0.91$ (9)	2.5
166	t-Bu	$CH(CH_3)_2$	$1.94 \times 10^{-4} \pm 0.97$ (4)	$1.14 \times 10^{-3} \pm 0.33$ (4)	$1.15 \times 10^{-4} \pm 0.21$ (4)	1.68
Metoprolol^{e}			$7.99 \times 10^{-7} \pm 1.34$ (4)	$1.94 \times 10^{-7} \pm 1.32$ (5)	$9.33 \times 10^{-5} \pm 0.21$ (4)	8.5×10^{-3}
Propranolol^{e}			$9.07 \times 10^{-7} \pm 1.41$ (26)	$3.19 \times 10^{-7} \pm 1.70$ (12)	ND^{f}	

[a] Molar concentration of β-adrenergic antagonist test compound required to induce a 50 % inhibition of heart rate for the right spontaneously beating atrium, the contractile activity of the left atrium and the trachea.

[b] Selectivity ratio (β_1/β_2)= [ID_{50}(right atrium) / ID_{50} (trachea)], when (β_1/β_2) <1, selective for heart; (β_1/β_2) > 1, selective for trachea; and non-selective when (β_1/β_2) ratio is 1.

[c] Number in parenthesis represents the number of experiments.

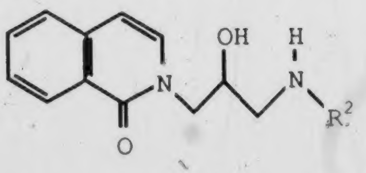
[d] Tissue stopped functioning at the same antagonist concentration using for the right atrium to reach to maximal response.

[e] Determined using the same assay as test compounds.

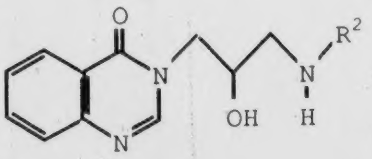
[f] Not determined.

However, compound (**164**), which is a pure (RS,SR) or (RR, SS) diastereomer is equipotent with (**161**). This result suggests the difference in potency between diastereomers may be small. The most logical explanation for the low activity is the absence of an ethereal oxygen atom which is present in propranolol. The distance between the terminal nitrogen and the dihydropyridyl ring is longer than that in class A arylethanolamines but shorter than that in class B aryloxypropanolamines. This explanation is also supported by the observation that replacement of the aryloxy moiety by a 1-isoquinolone or 4-quinazolinone ring system as in compounds (**255**, **256**, **259** and **260**) also resulted in low activity. The 1-isoquinolonyl or 4-quinazolinonyl moieties which are planar, were expected to possess a higher affinity for the β-adrenergic receptor than the dihydropyridyl moiety. However the test results in Table 33 indicate that the latter compounds exhibit low activities similar to the dihydropyridyl analogs described in Table 32. Compound (**260**) having a 3-(quinazolin-4-one) moiety exhibited a 3 to 4 fold decrease in pharmacological activity [1.63 x 10^{-3} M (right atrium); 5.09 x 10^{-4} M (left atrium); 1.0 x 10^{-2} M (trachea)] relative to the 2-(isoquinolin-1-one) (**255-256**).

Table 33. ID_{50} values for β-adrenergic antagonist activity of 1-[2-(isoquinolin-1-one)]-3-alkylamino-2-propanols and 1-[3-(quinazolin-4-one)]-3-alkylamino-2-propanols.



255-256



259-260

Compd.	R^2	Right atria ${}^{a}ID_{50} \pm SEM$ (β_1)	Left atria ${}^{a}ID_{50} \pm SEM$	Trachea ${}^{a}ID_{50} \pm SEM$ (β_2)	Selectivity ^{b}Ratio β_1/β_2
255	$C(CH_3)_3$	$4.70 \times 10^{-4} \pm 1.11$ (3)[c]	$1.74 \times 10^{-4} \pm 1.39$ (3)	$3.09 \times 10^{-3} \pm 1.09$ (3)	0.15
256	Cyclohexyl	$1.47 \times 10^{-4} \pm 1.19$ (6)	$1.47 \times 10^{-4} \pm 1.59$ (6)	$4.61 \times 10^{-4} \pm 1.26$ (6)	0.31
259	$CH(CH_3)_2$	$7.41 \times 10^{-4} \pm 1.34$ (3)	$1.87 \times 10^{-3} \pm 1.15$ (3)	$4.70 \times 10^{-2} \pm 1.01$ (3)	1.57×10^{-2}
260	$C(CH_3)_3$	$1.64 \times 10^{-3} \pm 1.19$ (3)	$5.09 \times 10^{-4} \pm 1.04$ (3)	$1.00 \times 10^{-2} \pm 1.09$ (3)	0.16
Metoprolol[d]		$7.99 \times 10^{-7} \pm 1.34$ (4)	$1.94 \times 10^{-7} \pm 1.32$ (5)	$9.33 \times 10^{-5} \pm 0.21$ (4)	8.50×10^{-3}
Propranolol[d]		$9.07 \times 10^{-7} \pm 1.41$ (26)	$3.19 \times 10^{-7} \pm 1.70$ (12)	ND[e]	

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[a] Molar concentration of β-adrenergic antagonist test compound required to induce a 50 % inhibition of the heart rate of the right spontaneously beating atrium, the contractile activity of the left atrium and the trachea. [b] Selectivity ratio (β_1/β_2)= [ID_{50}(right atrium) / ID_{50} (trachea)], when (β_1/β_2) <1, selective for heart; (β_1/β_2) > 1, selective for tracheas; and non-selective when (β_1/β_2) ratio is 1.

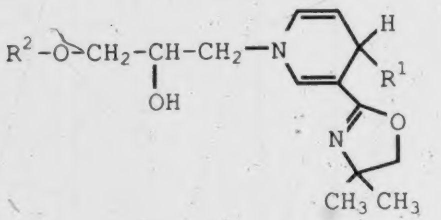
[c] Number in parenthesis represents number of experiments.

[d] Determined using the same assay as test compounds. [e] Not determined.

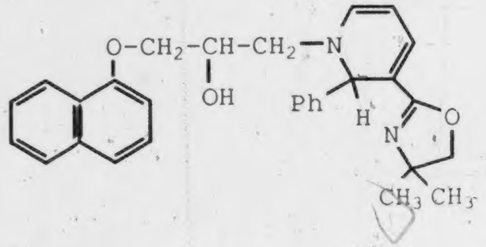
4.3.2.0.0 PHARMACOLOGICAL EVALUATION OF 1-ARYLOXY-3-{1-[4-ALKYL(PHENYL)-3-(4,4-DIMETHYLOXAZOLIN-2-YL)]-1,4-DIHYDROPYRIDYL}-2-PROPANOLS and 1-ARYLOXY-3-{1-[2-PHENYL-3-(4,4-DIMETHYLOXAZOLIN-2-YL)]-1,2-DIHYDROPYRIDYL}-2-PROPANOL.

Replacement of the terminal secondary alkylamino moieties of aryloxypropanolamines by a 1,2- or 1,4-dihydropyridine ring system, that is stabilized by a 3-(4,4-dimethyloxazol-2-yl) substituent, gave a number of compounds which were tested *in vitro* to determine the effect of the terminal dihydropyridine ring system upon β-adrenergic antagonist activity. The pharmacological test procedures were identical to those described previously in section 4.0.0.0.0. The ID_{50} values for selected compounds (**171**, **172**, **174**, **176** and **178**) are presented in Table 34. Compounds (**172** and **174**) are propranolol analogues in which the terminal N-substituent was replaced by a 1,2-(or 1,4-)dihydropyridine ring system. Compounds (**172** and **174**) are equipotent in the right atrium and trachea assays, although (**172**) was slightly more potent (3 times) in the left atrium relative to (**174**). Thus the 1,2- or 1,4-dihydropyridine ring system is not a useful terminal substituent for β-adrenergic antagonist activity. Compounds (**172**, **176**, **178**) possess a terminal 1,4-dihydropyridine ring where the C-4 R^1-substituents are Ph, n-Bu, and Me, respectively. The potency order of (**172**, **176**, **178**) was dependent upon the C-4 dihydropyridyl substituent where the relative order of activity was Ph < n-Bu < Me in right, left atrium and trachea. Compound (**172**), which is more lipophilic was less potent in the right, and left atrium and in trachea than (**176**, **178**). It appears that lipophilicity may be a significant determinant of activity in this *in*

Table 34. ID$_{50}$ values for β-adrenergic antagonist activity of 1-aryloxy-3-{1-[2-(or 4-)alkyl(or phenyl)-3-(4,4-dimethyloxazolin-2-yl)]-1,2-(or 1,4-)dihydropyridyl}-2-propanols.



171, 172, 176, 178



174

Compd.	R^1	R^2	Right atria (chronotropic effect) ^{a}ID$_{50}$ ± SEM (β$_1$)	Left atria (inotropic effect) ^{a}ID$_{50}$ ± SEM	Trachea (smooth muscle) ^{a}ID$_{50}$ ± SEM (β$_2$)	Selectivity Ratio β$_1$/β$_2$
171	Ph	Ph	$5.75 \times 10^{-5} \pm 0.83$ (4)^c	$4.26 \times 10^{-4} \pm 0.97$ (4)	$2.57 \times 10^{-5} \pm 0.89$ (6)	2.23
172	Ph	1-Naphthyl	$4.89 \times 10^{-4} \pm 0.85$ (3)	$7.07 \times 10^{-4} \pm 0.95$ (4)	$5.12 \times 10^{-4} \pm 0.91$ (4)	0.95
174	Ph	1-Naphthyl	$6.16 \times 10^{-4} \pm 0.33$ (3)	$2.23 \times 10^{-3} \pm 0.97$ (4)	$1.14 \times 10^{-4} \pm 0.93$ (6)	5.40
176	n-Bu	1-Naphthyl	$1.44 \times 10^{-4} \pm 0.81$ (3)	$1.44 \times 10^{-4} \pm 0.93$ (3)	$1.65 \times 10^{-5} \pm 0.87$ (8)	8.72
178	Me	1-Naphthyl	$1.20 \times 10^{-5} \pm 0.31$ (4)	$6.16 \times 10^{-5} \pm 0.58$ (4)	$9.50 \times 10^{-6} \pm 0.93$ (5)	1.26

Table 34. (cont.)

Metoprolol[d]	$7.99 \times 10^{-7} \pm 1.34$ (4)	$1.94 \times 10^{-7} \pm 1.32$ (5)	$9.33 \times 10^{-5} \pm 0.21$ (4)	8.5×10^{-3}
Propranolol[d]	$9.07 \times 10^{-7} \pm 1.41$ (26)	$3.19 \times 10^{-7} \pm 1.70$ (12)	ND[e]	

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[a] Molar concentration of β-adrenergic antagonist test compound required to induce a 50 % inhibition of heart rate of the right spontaneously beating atrium, the contractile activity of the left atrium and the trachea.

[b] Selectivity ratio (β_1/β_2)= [ID_{50}(right atrium) / ID_{50} (trachea)], when (β_1/β_2) <1, selective for heart; (β_1/β_2) > 1, selective for trachea; and non-selective when (β_1/β_2) ratio is 1.

[c] Number in parenthesis represents the number of experiments.

[d] Determined using the same assay as the test compounds.

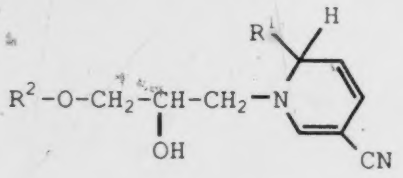
[e] Not determined.

vitro assay as it determines solubility. The low activity for this class of compounds could be the lack of hydrogen atom on the terminal nitrogen which may be important to the β-adrenergic receptor interaction.

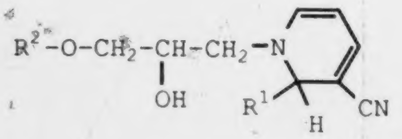
4.3.3.0.0 PHARMACOLOGICAL EVALUATION OF 1-ARYLOXY-3-{1-[2-ALKYL-3-CYANO]-1,2-DIHYDROPYRIDYL}-2-PROPANOLS AND 1-ARYLOXY-3-{1-[6-ALKYL-3-CYANO]-1,6-DIHYDROPYRIDYL}-2-PROPANOLS.

A similar replacement of the secondary alkylamino moiety of aryloxypropanolamines by a 1,2- or 1,6-dihydropyridine ring system, that is stabilized by a 3-cyano substituent, provided a number of compounds that were tested *in vitro* as β-adrenergic antagonists to determine the effect of a terminal dihydropyridine ring system upon β-adrenergic antagonist activity. The pharmacological test procedures used were identical to those described previously in section 4.0.0.0.0. The ID_{50} values for selected compounds (**179, 180, 181** and **182**) are presented in Table 35. The R^1 n-butyl compounds (**179**) and (**181**) were more potent than the corresponding R^1 t-butyl analogues (**180**) and (**182**) on right and left atria, which may be due to their lower lipophilicity. The 1,2-dihydropyridyl compounds were generally more active than the corresponding 1,6-dihydropyridyl isomer in the right atrial chronotropic and left atrial inotropic assays, although the activity of (**182**) was greater than (**180**) in the left inotropic assay. The weak β-adrenergic antagonist activity exhibited by compounds (**179-182**) is most likely due to the absence of a terminal amino hydrogen atom which may be involved in the receptor interaction.

Table 35. ID_{50} values for β-adrenergic antagonist activity of 1-aryloxy-3-{1-[2-(or 6-)alkyl-3-cyano-1,2-(or 1,6-)dihydropyridyl}-2-propanols.



179, 180



181, 182

Compd.	R^1	R^2	Right atria (chronotropic effect) [a]ID_{50} ± SEM (β_1)	Left atria (inotropic effect) [a]ID_{50} ± SEM	Trachea (smooth muscle) [a]ID_{50} ± SEM (β_2)	Selectivity [b]Ratio β_1/β_2
179	n-Bu	Ph	$1.51 \times 10^{-4} \pm 0.17$ (6)[c]	$3.08 \times 10^{-4} \pm 0.18$ (4)	$1.62 \times 10^{-4} \pm 0.11$ (10)	0.93
180	n-Bu	1-Naphthyl	$5.75 \times 10^{-4} \pm 0.75$ (4)	$4.16 \times 10^{-3} \pm 0.81$ (4)	$1.20 \times 10^{-4} \pm 0.69$ (4)	4.79
181	t-Bu	Ph	$6.76 \times 10^{-5} \pm 0.72$ (4)	$1.65 \times 10^{-4} \pm 0.87$ (4)	$1.65 \times 10^{-4} \pm 0.77$ (6)	0.40
182	t-Bu	1-Naphthyl	$2.23 \times 10^{-3} \pm 0.57$ (3)	$7.41 \times 10^{-4} \pm 0.97$ (3)	$1.0 \times 10^{-4} \pm 0.83$ (7)	22.3
Metoprolol[d]			$7.99 \times 10^{-7} \pm 1.34$ (4)	$1.94 \times 10^{-7} \pm 1.32$ (5)	$9.33 \times 10^{-5} \pm 0.21$ (4)	8.5×10^{-3}
Propranolol[d]			$9.07 \times 10^{-7} \pm 1.41$ (26)	$3.19 \times 10^{-7} \pm 1.70$ (12)	ND[e]	

[a] Molar concentration of β-adrenergic antagonist test compound required to induce a 50 % inhibition of heart rate of the right spontaneously beating atrium, the contractile activity of the left atrium and the trachea. [b] Selectivity ratio (β_1/β_2)= [ID_{50}(right atrium) / ID_{50} (trachea)], when (β_1/β_2) <1, selective for heart; (β_1/β_2) > 1, selective for trachea; and non-selective when (β_1/β_2) ratio is 1.
[c] Number in parenthesis represents the number of experiments. [d] Determined using the same assay as the test compounds.
[e] Not determined.

4.4.0.0.0 PHARMACOLOGICAL EVALUATION OF (R,S)-1-[QUINOL-5-, (4-, OR 2-)YLOXY]-3-ALKYLAMINO-2-PROPANOLS AND (R)- OR (S)-(QUINOLIN-5-YLOXY)-3-ALKYLAMINO-2-PROPANOLS.

4.4.1.0.0 PHARMACOLOGICAL EVALUATION OF (R,S)-1-[QUINOL-5, (4-, OR 2-)YLOXY]-3-ALKYLAMINO-2-PROPANOLS.

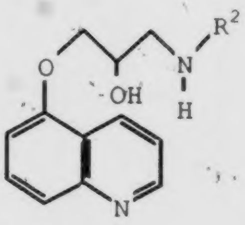
Replacement of the 1-nahpthyl ring of propranolol by a 5, 4, or 2-quinoline ring afforded (**211**, **233a**, and **242a**), respectively. The *in vitro* pharmacological test results (ID_{50} and pA_2 values) are presented in Table 36 and 37. The relative potency order for the isomeric quinolines based on ID_{50} and pA_2 values was (5-) **211** > (4-) **233a** > (2-) **242a** on atria. Thus, placement of the oxypropranolamine side chain at the 5-position of quinoline (**211**) afforded the most active compound which exhibited a 9 fold increase in activity on right atrium (1.03×10^{-7} M) and a 10 fold increase on the left atrium (3.55×10^{-8} M) relative to propranolol (9.07×10^{-7} M). Compound (**211**) was also the most cardioselective of these three compounds since it exhibited a 64 fold increase in cardioselectivity ($\beta_1/\beta_2 = 1.33 \times 10^{-4}$) relative to metoprolol ($\beta_1/\beta_2 = 8.5 \times 10^{-3}$). The corresponding pA_2 values listed in Table 37 also showed that compound (**211**) is the most active and cardioselective isomer in the atria and trachea assays. The pA_2 value of (**211**) is equipotent with the literature pA_2 value for propranolol on both atria and trachea and slightly less potent than our experimental pA_2 value. The relative activity order for the quinolyl positional isomers (5 > 4 > 2) in the atrial assays correlates with electron density on the oxygen atom. The electron density on the oxygen atom is reduced by the inductive and/or resonance effect of the quinolyl nitrogen atom where the relative effect is 2 > 4 > 5. This correlation confirms the reported finding that the unshared electron pair on oxygen is directly involved in the binding to the adrenergic receptor[233]. Replacement of the isopropyl substituent of (**211**) by a t-butyl or cyclohexyl substituent afforded (**212**) and (**213**), respectively. The ID_{50} values in Table 36 indicate the order of activity on right and left atria is (**211**) = (**212**) > (**213**). Compound (**212**) is equipotent to (**211**) on atria, but two-fold more active on trachea. The N-isopropyl (**211**) and N-t-butyl (**212**) analogues exhibited the highest β_1/β_2 selectivity. The selectivity ratios (β_1/β_2), based on ID_{50} values listed in Table 36, indicate the order of the β_1 selectivity is (**211**) > (**212**) > (**213**). Similarly, the order of activity and β_1-selectivity based on pA_2 values (see in Table 37) for atria is also (**211**)(isopropyl) > (**212**) (t-butyl) > (**213**) (cyclohexyl).

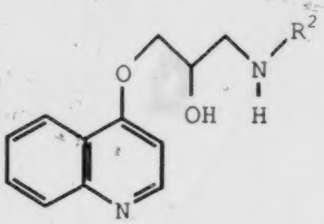
4.4.2.0.0 PHARMACOLOGICAL EVALUATION OF (R or S)-1-(QUINOl-5-YLOXY)-3-ISOPROPYL(or t-BUTYL)AMINO-2-PROPANOLS.

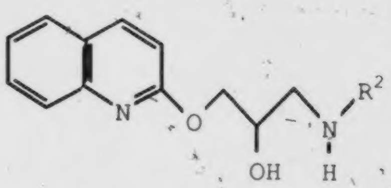
Class A, ethanolamines usually have the (-)-(R)-configuration, whereas the more active class B oxypropanolamines have the (-)-(S)-configuration[355,356]. Since (R,S)-(**211**) and (R,S)-(**212**) were the most active and cardioselective compounds, the (R)-1-(5-quinolinyloxy)-3-isopropyl(or t-butyl)amino-2-propanols (**214, 215**) and (S)-1-(5-quinolinyloxy)-3-isopropyl(or t-butyl)amino-2-propanols (**216, 217**) dihydrochloride salts were synthesized and tested *in vitro* as β-adrenergic antagonists to investigate the effect of the (R) or (S) configuration, relative to the racemates (**211**) and (**212**). The ID_{50} values for (**214-217**) are presented in Table 36. Compound (**214**) having the (R)-configuration was less potent than the racemate (**211**) or (S)-

(**216**) on atrial tissues. Compound (-)-(S)-(**216**) was equipotent with the racemate (**211**) but more potent than propranolol on both right and left atria. Compounds (S)-(**216**) and (R)-(**214**) are slightly less potent than the racemate (**211**). Typical dose-response curves for the right atria, which were used for the calculation of the ID_{50} values of (R,S)-(**211**), (S)-(**216**) and (R)- (**214**) are presented in Fig. 18. These results indicate the relative potency profile is (R,S)-(**211**) and (S)-(**216**) > (R)-(**214**). Replacement of the isopropyl moiety of (R)-(**214**) by a t-butyl group gave (**215**) which exhibited a two fold decrease in activity on right atrium, was equipotent on left atrium and was more active on trachea. In contrast, replacement of the isopropyl moiety of (**216**) by a t-butyl group afforded (**217**) which exhibited a slight decrease in activity on both right and left atria, but exhibited an increase in activity on trachea. A general correlation was observed where there was a decrease β_1/β_2-selectivity when the N-isopropyl substituent (**211**, **214**, **216**) was replaced by N-t-butyl substituent (**212**, **215**, **217**).

Table 36. ID_{50} values for β-adrenergic antagonist activity of (R,S), (R), or (S)-1-(5'-quinolyloxy)-3-alkylamino-2-propanols and (R,S)-1-[4-(or 2-)quinolyloxy]-3-alkylamino-2-propanols.


211-213; 214-222


233


242 (a,b)

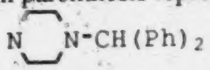
Compd.	R^2	Configuration	Right atria $^aID_{50}$ ± SEM (β_1)	Left atria $^aID_{50}$ ± SEM	Trachea $^aID_{50}$ ± SEM (β_2)	Selectivity ^{b}Ratio β_1/β_2
211	$CH(CH_3)_2$	R,S	1.03 x 10^{-7} ± 1.14 (3)^c	3.55 x 10^{-8} ± 1.39 (3)	7.70 x 10^{-4} ± 1.08 (3)	1.33 x 10^{-4}
212	$C(CH_3)_3$	R,S	1.04 x 10^{-7} ± 1.17 (3)	3.09 x 10^{-8} ± 1.26 (3)	3.69 x 10^{-4} ± 1.09 (3)	2.80 x 10^{-4}
213	Cyclohexyl	R,S	6.70 x 10^{-6} ± 1.42 (6)	1.52 x 10^{-6} ± 1.58 (9)	4.57 x 10^{-4} ± 1.22 (8)	1.46 x 10^{-2}
242a	$CH(CH_3)_2$	R,S	1.41 x 10^{-5} ± 1.17 (6)	4.68 x 10^{-6} ± 1.51 (6)	1.86 x 10^{-4} ± 2.53 (6)	7.58 x 10^{-2}
242b	$C(CH_3)_3$	R,S	2.07 x 10^{-5} ± 1.32 (6)	4.57 x 10^{-6} ± 1.38 (6)	1.12 x 10^{-3} ± 1.56 (6)	1.84 x 10^{-2}
233	$CH(CH_3)_2$	R,S	1.39 x 10^{-5} ± 1.68 (9)	1.29 x 10^{-6} ± 1.41 (7)	3.31 x 10^{-3} ± 2.72 (4)	4.19 x 10^{-3}

Table 36. (cont.)

Compd.	R^2	Configuration	Right atria ${}^aID_{50} \pm SEM\ (\beta_1)$	Left atria ${}^aID_{50} \pm SEM$	Trachea ${}^aID_{50} \pm SEM\ (\beta_2)$	Selectivity ^{b}Ratio β_1/β_2
214[d]	$CH(CH_3)_2$	R	$2.34 \times 10^{-6} \pm 1.06$ (3)[c]	$3.92 \times 10^{-7} \pm 1.16$ (3)	$1.47 \times 10^{-3} \pm 1.17$ (3)	1.59×10^{-3}
215[d]	$C(CH_3)_3$	R	$4.33 \times 10^{-6} \pm 1.18$ (3)	$3.98 \times 10^{-7} \pm 1.02$ (3)	$6.21 \times 10^{-4} \pm 1.17$ (3)	6.97×10^{-3}
216[d]	$CH(CH_3)_2$	S	$1.74 \times 10^{-7} \pm 1.08$ (3)	$2.09 \times 10^{-8} \pm 1.22$ (3)	$1.34 \times 10^{-3} \pm 1.03$ (3)	1.26×10^{-4}
217[d]	$C(CH_3)_3$	S	$1.77 \times 10^{-7} \pm 1.18$ (3)	$3.74 \times 10^{-8} \pm 1.27$ (3)	$4.07 \times 10^{-4} \pm 1.41$ (3)	4.34×10^{-4}
218	Cyclohexyl	S	$1.22 \times 10^{-6} \pm 1.40$ (3)	$2.34 \times 10^{-8} \pm 1.22$ (3)	$3.78 \times 10^{-4} \pm 1.04$ (3)	3.22×10^{-3}
220	Indolyl-t-Bu	S	$8.84 \times 10^{-7} \pm 1.40$ (3)	$2.39 \times 10^{-7} \pm 1.22$ (5)	$1.73 \times 10^{-4} \pm 1.04$ (10)	5.10×10^{-3}
221	(S)-[CH(MePh)]	S	$3.95 \times 10^{-6} \pm 1.46$ (3)	$5.38 \times 10^{-7} \pm 1.05$ (3)	$7.49 \times 10^{-5} \pm 1.11$ (6)	5.27×10^{-2}
222	[e]NH-R^2	S	$2.86 \times 10^{-5} \pm 1.53$ (6)	$1.83 \times 10^{-5} \pm 2.73$ (6)	$1.38 \times 10^{-4} \pm 1.30$ (6)	2.0×10^{-1}
Metoprolol[f]			$7.99 \times 10^{-7} \pm 1.34$ (4)	$1.94 \times 10^{-7} \pm 1.32$ (5)	$9.33 \times 10^{-5} \pm 0.21$ (4)	8.5×10^{-3}
Propranolol[d,f]			$9.07 \times 10^{-7} \pm 1.41$ (26)	$3.19 \times 10^{-7} \pm 1.70$ (12)	ND[g]	

[a] Molar concentration of β-adrenergic antagonist test compound required to induce a 50 % inhibition of heart rate of the right spontaneously beating atrium, the contractile activity of the left atrium and the trachea. [b] Selectivity ratio (β_1/β_2)= [ID_{50}(right atrium) / ID_{50} (trachea)], when $(\beta_1/\beta_2) <1$, selective for heart; $(\beta_1/\beta_2) > 1$, selective for trachea; and non-selective when (β_1/β_2) ratio is 1. [c] Number in parenthesis represents the number of experiments. [d] Compounds were tested as the dihydrochloride salts.

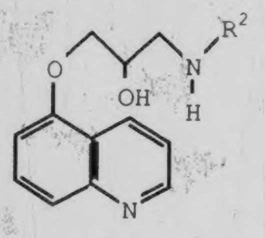
[e] NH-R^2 =



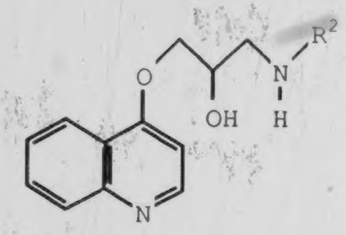
[f] Determined using the same assay as the test compounds.

[g] Not determined.

Table 37. pA_2 values for β-adrenergic antagonist activity of (R,S), (R), or (S)-1-(5-quinolyloxy)-3-alkylamino-2-propanols and (R,S)-1-[4-(or 2-)quinolyloxy]-3-alkylamino-2-propanols.



211-213; 214-222



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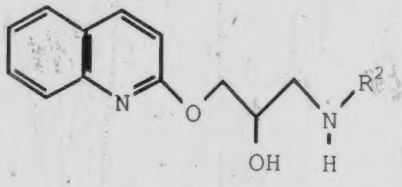


242 (a,b)

Compd.	R^2	Configuration	Right atria pA_2 ± SEM (β_1)	Left atria pA_2 ± SEM	Trachea pA_2 ± SEM (β_2)	[a]Selectivity Ratio β_1/β_2
211	$CH(CH_3)_2$	R,S	8.52 ± 0.25	9.01 ± 0.13	8.43 ± 0.16	-0.9[b]
212	$C(CH_3)_3$	R,S	7.83 ± 0.08	7.93 ± 0.08	9.22 ± 0.88	13.9[c]
213	Cyclohexyl	R,S	7.01 ± 0.05	7.34 ± 0.11	8.50 ± 0.82	15.0
242a	$CH(CH_3)_2$	R,S	6.45 ± 0.09	6.83 ± 0.05	7.17 ± 0.14	7.2
242b	$C(CH_3)_3$	R,S	6.14 ± 0.07	6.22 ± 0.06	6.90 ± 0.17	7.6
233	$CH(CH_3)_2$	R,S	8.35 ± 0.55	T[d]	T[d]	

Table 37. (cont.)

Compd.	R^2	Configuration	Right atria pA_2 ± SEM (β_1)	Left atria pA_2 ± SEM	Trachea pA_2 ± SEM (β_2)	[a]Selectivity Ratio β_2/β_1
214	$CH(CH_3)_2$	R	7.51 ± 0.07	7.26 ± 0.18	7.57 ± 0.4	0.60[b]
215	$C(CH_3)_3$	R	7.42 ± 0.20	6.92 ± 0.34	8.19 ± 0.23	7.70
216	$CH(CH_3)_2$	S	9.11 ± 0.03	9.10 ± 0.14	8.44 ± 1.01	-6.7[c]
217	$C(CH_3)_3$	S	8.59 ± 0.03	8.68 ± 0.07	13.3 ± 0.85	47.1
218	Cyclohexyl	S	7.73 ± 0.32	7.38 ± 0.09	6.30 ± 0.22	-14.3
220	Indolyl-t-Bu	S	9.81 ± 0.25	T[d]	T	
221	(S)-[CH(MePh)]	S,S	7.81 ± 0.13	8.45 ± 0.06	5.85 ± 0.16	-19.6
Propranolol[e]			9.32 ± 0.24	9.69 ± 1.09	9.46 ± 0.11	1.40
Propranolol[f]			8.62 ± 0.17		8.47	-1.50
Propranolol[g]			8.7		8.9	2.0
Metoprolol[e]			7.68 ± 0.20	7.55 ± 1.11	7.90 ± 0.67	2.2

[a] Selectivity ratio (β_1/β_2)= 10[pA_2(trachea)-pA_2(right atrium)],[464] [b] Selective for heart, +[c] Selctive for trachea.

[d] Tissue was stopped functioning at an antagonist concentration of 1 x 10^{-4} M.

[e] pA_2 values from our experiment. [f] pA_2 value from the literature[463]. [g] pA_2 value from the literature[464].

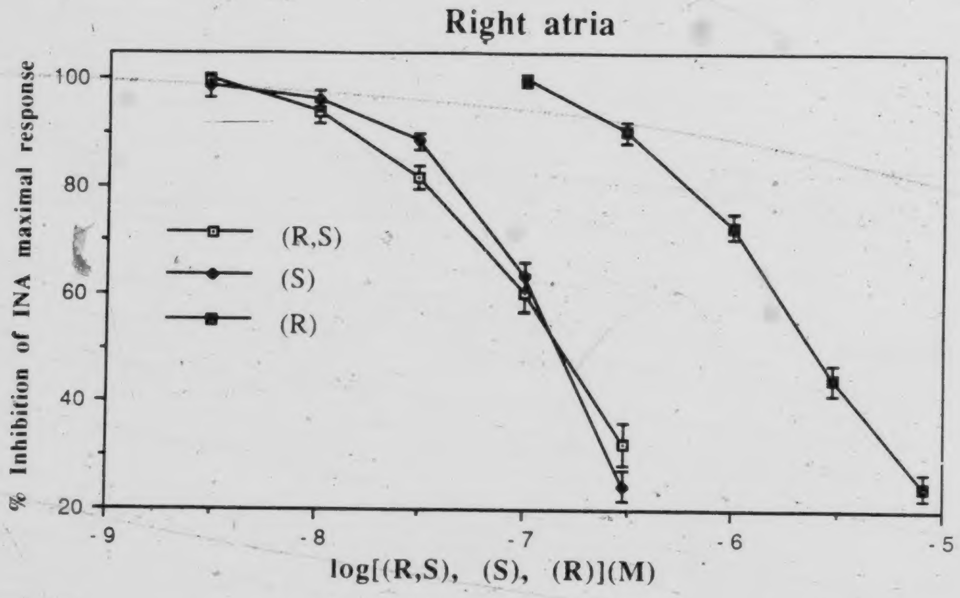


Fig.18. Dose-response curves illustrating the pharmacological activity of compounds possessing the (R,S)-(**211**), (S)-(**216**) and (R)-(**214**) configurations. Each point represents the mean of 3 experiments ± SEM.

The above results are generally in agreement with existing knowledge pertaining to the stereoselectivity of β-adrenoceptor antagonists. Thus, the most potent β-adrenoceptor antagonist activity is exhibited by the (-)-enantiomer having the (S) absolute configuration for class B oxypropranolamines. A comparison of ID_{50} values for right and left atria, and trachea for compounds (**211-212**, **214-215**, and **216-217**) having the (RS), (R) and (S) configuration relative to metoprolol are presented in Fig. 19.

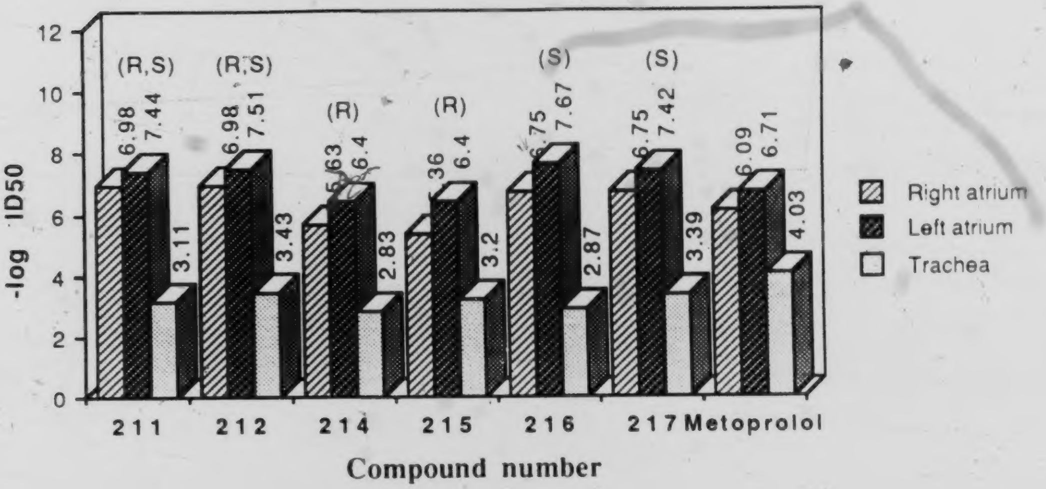


Fig. 19. Comparison of the -log ID_{50} values for (R,S)-(**211**, **212**), (R)-(**214**, **215**) and (S)-(**216**,**217**) with metoprolol.

Examination of the pA_2 values of (**214-217**) listed in Table 37 indicate that compounds having the (R)-configuration are less potent than compounds having the (R,S)- and (S)-configurations on atria (see Fig. 20). This observation is in agreement with the ID_{50} values illustrated in Fig. 19. The pA_2 value for compound (-)-(S)-(**216**) indicates it is more active than the racemate (**211**), (R)-(**214**), equipotent with propranolol (experimental pA_2 value) and more active than propranolol (literature pA_2 value) on both right and left atrium. Compound (-)-(S)-(**216**) displays the highest cardioselective ratio (-6.7) compared to (R,S)-(**211**)(-0.9) and (R)-(**214**)(0.60).

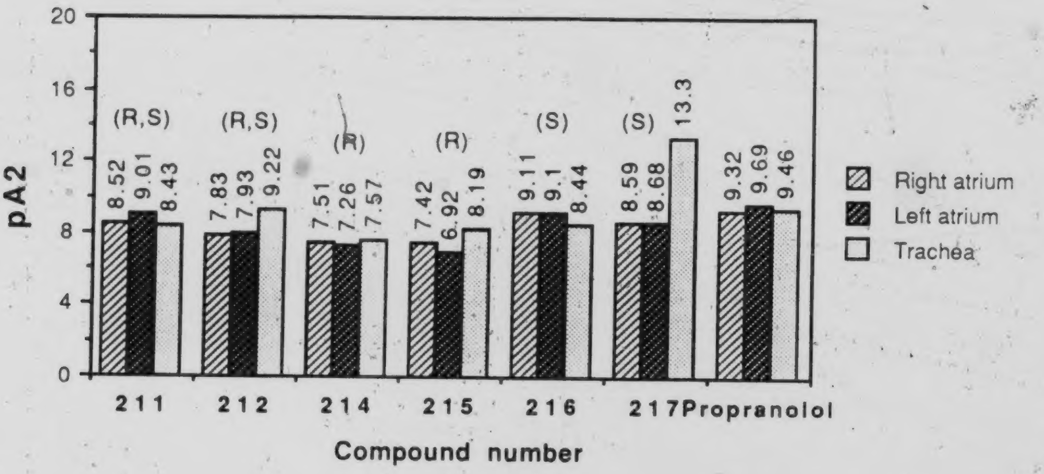
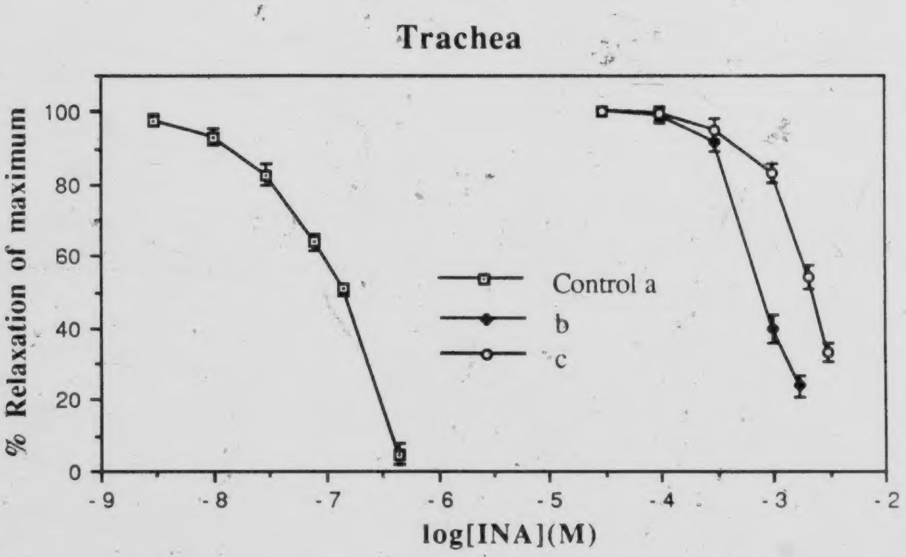


Fig. 20. Comparison of the pA_2 values for (R,S)-(**211, 212**), (R)-(**214, 215**) and (S)-(**216,217**) with propranolol.

The markedly different values for the cardioselective ratio between the ID_{50} (Fig.19) and pA_2 values (Fig. 20) is likely due to the high antagonist dose used on trachea which required a very high concentration of isoproterenol (INA) to displace the antagonist at the β-receptor. Compound (**217**) was 2300 times more selective for the β_1 relative to the β_2-receptor from the ID_{50} calculation. In contrast, it was more selective for the β_2 relative to the β_1-receptor from the pA_2 calculation. These diametrically opposite results are attributed to a non-parallel shift of the dose-response curve to the right when the antagonist concentration is increased (Fig. 21). This is likely due to the high concentration of (**217**) used in the assay (3×10^{-5} to 3×10^{-4} M range) as explained above. The results in Fig. (19,20) indicate that (R)-(**214**) is equipotent with (S)-(**216**) on tracheal tissue.



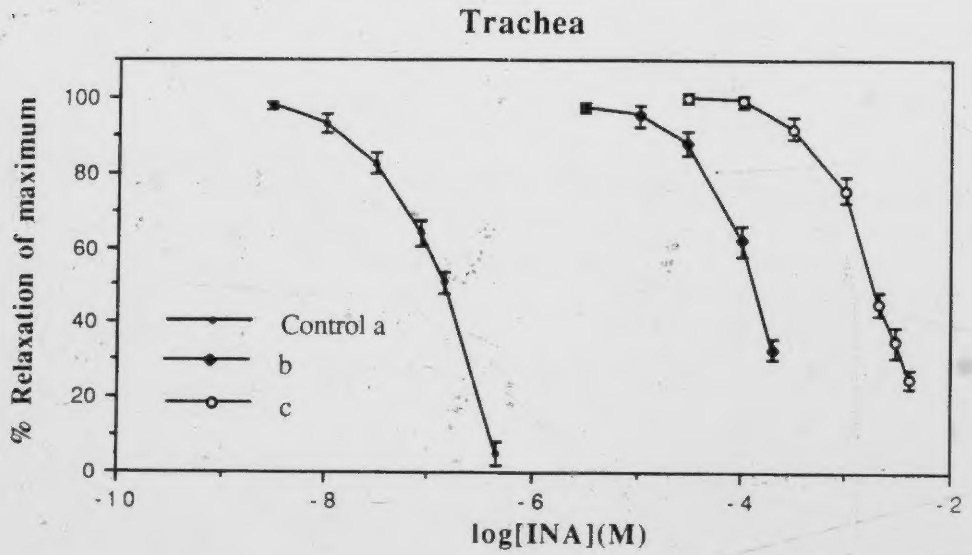
a= Control curve for INA

b= Control curve for INA in the presence of 3 x 10^{-5} M antagonist (**217**)

c= Control curve for INA in the presence of 3 x 10^{-4} M antagonist (**217**)

Fig. 21. Dose-response curves of INA without and in the presence of antagonist (**217**). Each point represents the mean of 3 experiments ± SEM.

A parallel shift of the dose-response curve to the right for (**216**) on trachea, when the concentration of antagonist (**216**) was increased ten times (5 x 10^{-6} to 5 x 10^{-5} M), required a ten fold higher concentration of agonist (INA) to the same response relative to when the antagonist was absent (see Fig. 22a); similar results were found on atria (see Fig. 22b). Compound (**216**) is considered to be a competitive adrenergic antagonist.

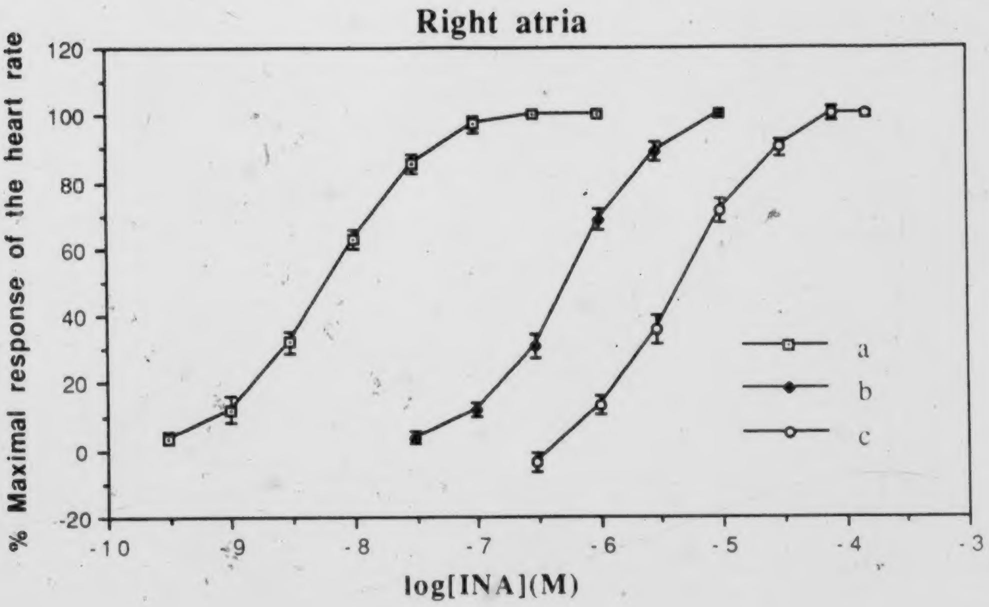


a= Control curve for INA

b= Control curve for INA in the presence of 5 x 10^{-6} M antagonist (**216**)

c= Control curve for INA in the presence of 5 x 10^{-5} M antagonist (**216**)

Fig. 22a. Dose-response curves for INA without and in the presence of the antagonist (S)-(**216**) for trachea. Each point represents the mean of 3 experiments ± SEM.



a= Control curve for INA

b= Control curve for INA in the presence of 5 x 10^{-8} M antagonist (**216**)

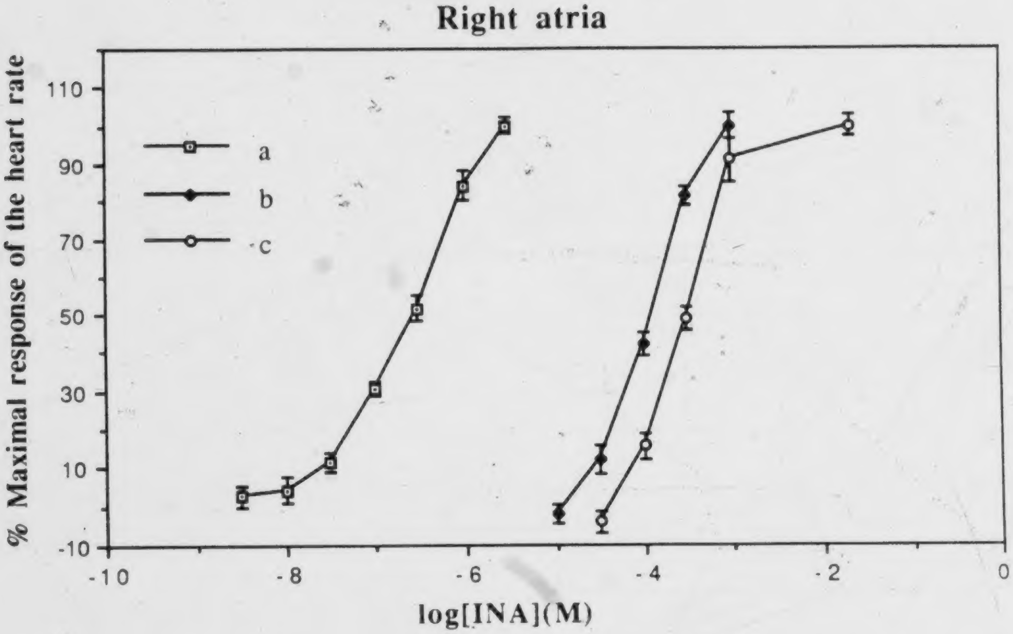
c= Control curve for INA in the presence of 5 x 10^{-7} M antagonist (**216**)

Fig. 22b. Dose-response curves for INA without and in the presence of the antagonist (S)-(**216**) for right atrium. Each point represents the mean of 3 experiments ± SEM.

4.4.3.0.0 PHARMACOLOGICAL EVALUATION OF (S)-1-(5-QUINOLINYLOXY)-3-ALKYL(ARYL)AMINO-2-PROPANOLS.

Compound (S)-(**216**) is the most active and cardioselective β-adrenergic antagonist prepared in this study. It was therefore of interest to replace the substituent on the basic amino group of (**216**) by different alkyl and heteroaryl groups to develop more selective and potent compounds. A number of analogues of (**216**) were synthesized (**218**,

220, 221, 222) which were subjected to pharmacological evaluation. The ID_{50} and pA_2 values for (**218, 220, 221, 222**) are listed in Tables 36 and 37. Replacement of the isopropyl substituent of (S)-(**216**) by cyclohexyl gave (S)-(**218**) which was more potent on atria than the racemate (**213**) (see Table 36). (S)-(**218**) was also more selective for the β_1-receptor than the racemate (**213**). The pA_2 values for (S)-(**218**) listed in Table 37 showed a similar profile of activity. The results indicate that elaboration of (S)-(**216**), in which the amino substituent on the side chain is replaced by a more steric and/or lipophilic group, than than isopropyl moiety affords less potent and more cardioselective compounds. Similar results were observed for the indolyl-tert-butyl compound (S)-(**220**). Compound (S)-(**220**) exhibited a five fold decrease in activity on right atrium (8.84×10^{-7} M) relative to (S)-(**216**) (1.74×10^{-7} M) (see Table 36), but compound (S)-(**220**) was slightly more potent ($pA_2 = 9.81$) than (S)-(**216**) ($pA_2 = 9.11$) (see Table 37). This difference may be attributed to the sensitivity of the tisuue, since the tissue responded at a maximal dose for INA (3×10^{-6} M) which was higher than the normal control dose INA (3×10^{-7} M) causing a decrease in activity (ID_{50}). The high maximal control dose of INA did not affect the calculation of the pA_2 value when the dose-response curve shifted to the right as illustrated in Fig 23.



a= Control curve for INA with maximal concentration (3 x 10^{-6} M)

b= Control curve for INA in the presence of 7 x 10^{-7} M antagonist (**220**)

c= Control curve for INA in the presence of 2 x 10^{-6} M antagonist (**220**)

Fig. 23. Dose-response curves for INA without and in the presence of antagonist (**220**). Each point represents the mean of 3 experiments ± SEM.

It is known that the incorporation of a second chiral substituent onto the class A ethanolamine side chain gave rise to four diastereomers in which the (S_a,R_b) diastereomer was more potent than the complete mixture (S_a is the absolute configuration of CH(OH), and R_b is the absolute configuration of the second chiral carbon).[162] Thus, it was of interest to replace the isopropyl substituent of (S)-(**216**) by a second chiral (S)-α-methylbenzyl substituent which would yield (S,S)-(**221**) to determine the effect upon class B β-adrenergic blocking activity. The ID_{50} and pA_2 results in Table 36 and 37, indicate that (S,S)-(**221**) was less potent than (S)-(**216**) and propranolol in reducing chronotropic (right atria) and inotropic (left atria) activity. (S,S)-(**221**) exhibited a greater β_1-selectivity (heart) than (S)-(**216**) and propranolol (see Table 37). This result indicated that the second (S)-chiral center may enhance affinity for the β_1-receptor. Since the (S,R) diastereomer was not synthesized for comparison with (S,S)-(**221**), the pharmacological results just described for (S,S)-(**221**) are to be considered as preliminary. Replacement of the isopropyl moiety of (S)-(**216**) by a N^4-benzhydrylpiperazinyl group provided (S)-(**222**). (S)-(**222**) was significantly less potent than (S)-(**216**) with respect to its ability to reduce chronotropic and inotropic activity. The cardioselectivity of (S)-(**222**) was also reduced markedly relative to (S)-(**216**). This reduction in potency on both atria and trachea may be due to the absence of an amino hydrogen which could be required for the receptor interaction. A similar result was described previously for compounds lacking an amino hydrogen substituent (see section 4.3.2.0.0). The pA_2 value for (S)-(**222**) was not determined in view of its low activity and non-selectivity for β-adrenergic receptors. A summary of the pA_2 values for the 5-quinoline substituted analogues are presented in Fig. 24. These pharmacological results indicated that the most β_1-selective compounds were in the order of **211** < **216** < **218** < **221**. The order of activity on atria based on configuration was (S)-(**216**) > (R,S)-(**211**) > (R)-(**214**) or (S)-(**217**) > (R,S)-(**212**) > (R)-(**215**). When the size of the N-substituent was increased, the activity on trachea was increased in the order ((R,S)-**211** < (R,S)-**212** < (R,S)-**213**, or (R)-**214** < (R)-**215**, but was decreased for (S)-configuration compounds where the potency order was (S)-**211** > (S)-**218** > **221**.

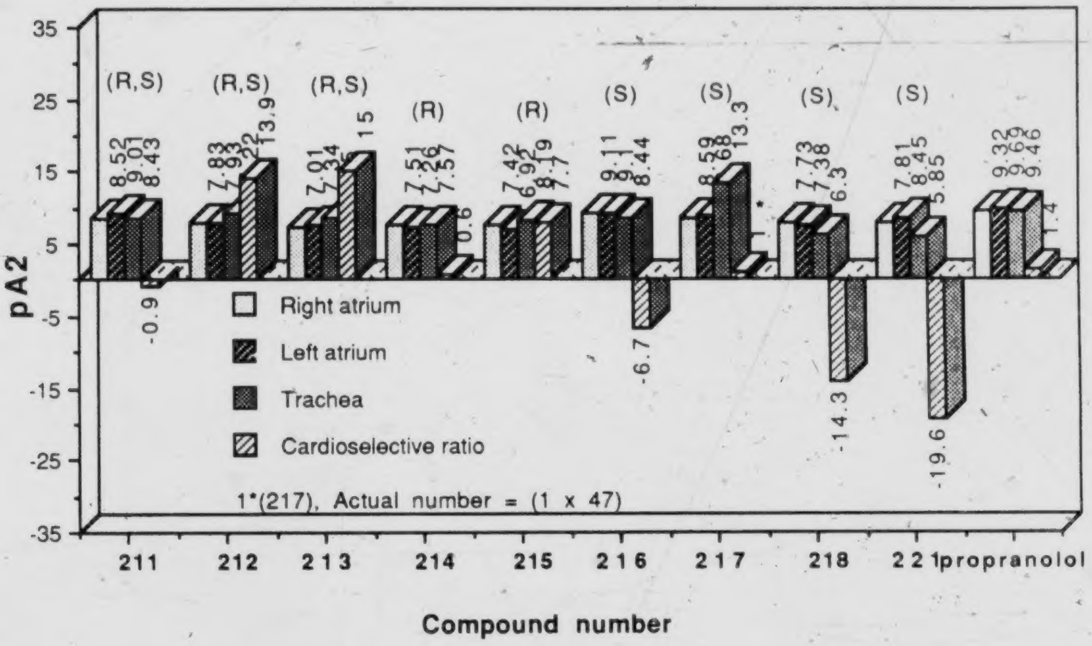


Fig. 24. A summary of the pA_2 values for 5-quinoline substituted analogues.

4.5.0.0.0 PHARMACOLOGICAL EVALUATION OF (R,S)-1-(PYRIMDIN-2-YLOXY)-3-ALKYLAMINO-2-PROPANOLS (245a,b).

Pyrimidine could be an isostere of 3-cyano or nitropyridine (**112**)[382]. A study was therefore initiated to replace the 3-cyanopyridine ring of (**112**) by a 2-pyrimidinyl ring to determine the effect upon β-adrenergic antagonist activity. Two compounds (**245 a,b**), which are analogues of (**112**), were prepared and tested using the test procedures described in section 4.0.0.0.0. The ID_{50} and pA_2 values for (**245 a,b**) are presented in Tables 38 and 39. Compound (**245a**) was about ten fold less effective in reducing chronotropic and inotropic activity relative to propranolol (see Table 38). Compound (**245a**) also possessed a high cardioselectivity with a β_1/β_2 ratio = 2.28×10^{-4}. The results for (**245a**) as illustrated by the pA_2 values for atria and trachea in Table 39, are similar with high cardioselectivity β_1/β_2 ratio = -10.7 relative to (S)-(**216**) (-6.7) . Replacement of the isopropyl substituent (**245a**) by a t-butyl group gave (**245b**) which was less effective in reducing chronotropic activity but more effective in reducing inotropic activity than (**245a**). The cardioselectivity of (**245b**) was also less than that of (**245a**). The pA_2 for (**245b**) for atria that are summarized in Table 39 are similar. The abnormal pA_2 = 29.3 value for (**245b**) on trachea was attributed to the high concentration of antagonist used and a non-parallel shift of dose response curve as described previously in section 4.4.2.0.0 (Fig.21).

4.6.0.0.0 PHARMACOLOGICAL EVALUATION OF (R,S)-1-(ISOQUINOLIN-5-YLOXY)-3-ALKYLAMINO-2-PROPANOLS.

Most structural modifications employed for the improvement of β-adrenoceptor affinity and selectivity have involved aromatic ring substituents, but more recently, a variety of substituents on the basic amino group have also been studied. The nature and position of aromatic substituents has been shown to dramatically influence the pharmacological profile. In recent years, the electronic features of β-adrenergic agents belonging to the three classes of adrenergic agents;

namely class A ethanolamines; class B aryloxypropanolamines; and class C oxime ethers have been reported[465]. The electronic features for the class B compounds are illustrated in Fig. 25.

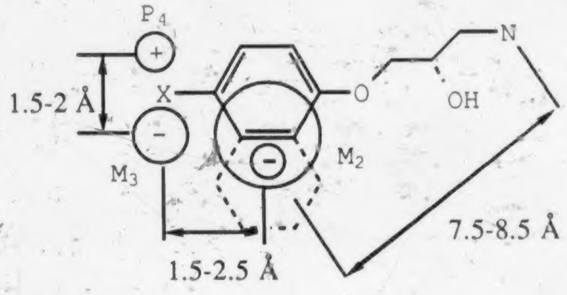


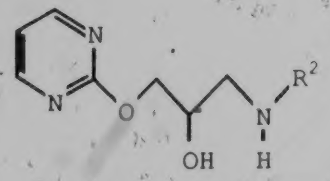
Fig. 25. The regional electronic features for class B aryloxypropanolamines.

In the solid state, it has been observed that the conformation of the side chain present in aryloxypropanolamines is consistently found in an extended conformation[465] as illustrated in Fig. 24. A negative potential can be induced by either the side chain or the aromatic region of the molecule. A negative minimum in the M_2 region is an essential feature for binding to the β-adrenergic receptor. A negative minimum in the M_3 region is required for β_1-selective full and partial agonist activity. A positive maximum (P_4) is an additional requirement in the M_3 region for β_1-selective antagonist activity. In view of these various electronic regions present on an aromatic ring, a study to investigate the electronic features of a second fused ring was initiated. In an earlier series of 5-quinolinyl compounds, the quinolinyl nitrogen atom could have provided the negative minimum in the M_2 or M_3 region. The pharmacological results support this hypothesis since the 5-quinolinyl analogue (**211**) exhibited potent cardioselective activity relative to propranolol. We now describe further studies in which the 5-quinoline ring is replaced by an isoquinoline ring to provide compounds (**248, 249** and **250**). The ID_{50} and pA_2 values for (**248, 249** and **250**) are presented in Tables 38 and 39. Compound (**248**) exhibited a ten fold decrease in its ability to reduce chronotropic and inotropic activity relative to (**211**). The β_1-selectivity of (**248**) was also reduced markedly relative to (**211**). This result confirms that a negative minimum in the M_2 region is associated with the potency and selectivity of these β-antagonists. Modification of (**248**) by replacing the isopropyl moiety by a t-butyl or cyclohexyl gave (**249** or **250**), respectively. The pA_2 values (Table 39) indicate that the relative potency order is (**249**) > (**248**) > (**250**) with respect to their ability to reduce chronotropic and inotropic activity. The β_1-selectivity profile was (**250**) (-1.5) > (**249**) (1.4) > (**248**) (5.3). These results indicate that larger and/or more lipophilic substituents on side chain nitrogen enhance β_1-selectivity.

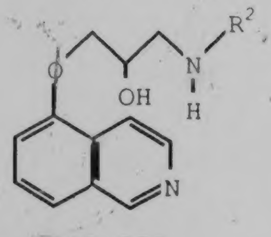
4.7.0.0.0 STRUCTURE-ACTIVITY RELATIONSHIPS FOR ARYLOXY (HETEROARYLOXY)PROPANOLAMIMES AS β-ADRENOCEPTOR ANTAGONISTS

The general structure of aryloxypropanolamines such as propranolol (**7**) was elaborated by replacing the aryl ring by various heteroaryl rings and/or the terminal amino moiety by sterically larger and/or lipophilic groups. Some general structure-activity correlations have been acquired which are summarized below based on β_1/β_2-adrenergic antagonist pharmacological results.

Table 38. ID_{50} values for β-adrenergic antagonist activity of (R,S)-1-(pyrimidin-2-yloxy)-3-alkylamino-2-propanols and (R,S)-1-(isoquinolin-5-yloxy)-3-alkylamino-2-propanols .



245 (a,b),



248-250

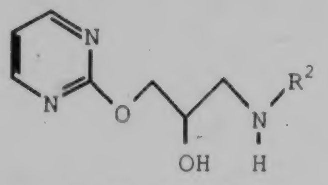
Compd.	R^2	Right atria $^{a}ID_{50} \pm SEM$ (β_1)	Left atria $^{a}ID_{50} \pm SEM$	Trachea $^{a}ID_{50} \pm SEM$ (β_2)	Selectivity ^{b}Ratio β_1/β_2
245a	$CH(CH_3)_2$	$1.02 \times 10^{-5} \pm 1.56$ (8)^{c}	$2.23 \times 10^{-6} \pm 1.67$ (8)	$4.47 \times 10^{-2} \pm 1.31$ (3)	2.28×10^{-4}
245b	$C(CH_3)_3$	$2.11 \times 10^{-5} \pm 1.11$ (3)	$2.27 \times 10^{-6} \pm 1.65$ (3)	$1.93 \times 10^{-3} \pm 1.12$ (3)	1.0×10^{-2}
248	$CH(CH_3)_2$	$1.10 \times 10^{-6} \pm 1.41$ (9)	$2.77 \times 10^{-7} \pm 1.19$ (9)	$7.84 \times 10^{-4} \pm 1.65$ (9)	1.40×10^{-3}
249	$C(CH_3)_3$	$1.23 \times 10^{-6} \pm 1.31$ (6)	$2.12 \times 10^{-7} \pm 1.11$ (3)	$7.94 \times 10^{-4} \pm 1.11$ (4)	1.54×10^{-3}
250	Cyclohexyl	$4.88 \times 10^{-5} \pm 1.162$ (6)	$7.92 \times 10^{-6} \pm 1.85$ (6)	$2.92 \times 10^{-4} \pm 1.13$ (3)	1.67×10^{-1}
Metoprolol^{d}		$7.99 \times 10^{-7} \pm 1.34$ (4)	$1.94 \times 10^{-7} \pm 1.32$ (5)	$9.33 \times 10^{-5} \pm 0.21$ (4)	8.50×10^{-3}
Propranolol^{d}		$9.07 \times 10^{-7} \pm 1.41$ (26)	$3.19 \times 10^{-7} \pm 1.70$ (12)	ND^{e}	

[a] Molar concentration of β-adrenergic antagonist test compound required to induce a 50 % inhibition of heart rate of the right spontaneously beating atrium, the contractile activity of the left atrium and the trachea.[b] Selectivity ratio (β_1/β_2)= [ID_{50}(right atrium) / ID_{50} (trachea)], when (β_1/β_2) <1, selective for heart; (β_1/β_2) > 1, selective for tracheas; and non-selective when (β_1/β_2) ratio is 1.

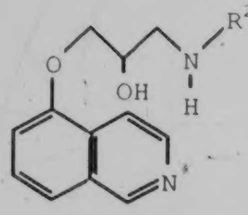
[c] Number in parenthesis represents the number of experiments.[d] Determined iusing the same assay as the test compounds.

[e] Not determined.

Table 39. pA_2 values for β-adrenergic antagonist activity of (R,S)-1-(pyrimidin-2-yloxy)-3-alkylamino-2-propanols and (R,S)-1-(isoquinolin-5-yloxy)-3-alkylamino-2-propanols .



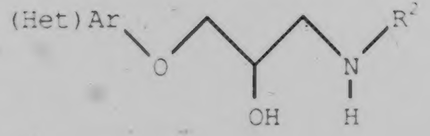
245 (a,b)



248-250

Compd.	R^2	Right atria $pA_2 \pm SEM$ (β_1)	Left atria $pA_2 \pm SEM$	Trachea $pA_2 \pm SEM$ (β_2)	[a]Selectivity Ratio β_1/β_2
245a	$CH(CH_3)_2$	8.58 ± 0.49	7.30 ± 0.26	7.51 ± 0.52	-10.7[b]
245b	$C(CH_3)_3$	6.45 ± 0.07	6.64 ± 0.14	29.3 ± 4.27	-22.8
248	$CH(CH_3)_2$	7.11 ± 0.05	7.56 ± 0.16	7.64 ± 0.34	5.3[c]
249	$C(CH_3)_3$	7.82 ± 0.05	8.59 ± 0.22	7.96 ± 0.19	1.4
250	Cyclohexyl	5.59 ± 0.15	5.71 ± 0.07	5.44 ± 0.15	-1.5
Propranolol[d]		9.32 ± 0.24	9.69 ± 1.09	9.46 ± 0.11	1.4
Propranolol[e]		8.62 ± 0.17		8.47	-1.5
Propranolol[f]		8.7		8.9	2.0
Metoprolol[d]		7.68 ± 0.20	7.55 ± 1.11	7.90 ± 0.67	2.2

[a] Selectivity ratio (β_1/β_2)= 10[pA_2(trachea)-pA_2(right atrium)],[464] - [b] Selective for heart, +[c] Selctive for trachea. [d] pA_2 values from our experiment. [e] pA_2 value from the literature[463]. [f] pA_2 value from the literature[464].



(7)

A) β-Adrenergic antagonist structure-activity correlations were obtained for selected compounds of general structure (**7**) where the aryloxy group was replaced by a:

1) 4-n-Butyl-3-(4,4-dimethyloxazolin-2-yl)-1,4-dihydropyridine moiety and R^2 was an isopropyl or t-butyl group (**148-149**). The pharmacological results indicated that (**148-149**) are weak β-adrenergic antagonists on heart and trachea (10^{-4} M range) relative to propranolol (10^{-7} M range), and that they do not exhibit any β_1/β_2-selectivity.

2) 2-(or 6)-n-Butyl(or t-butyl)-3-cyano-1,2-(or 1,6-)dihydropyridine ring system and R^2 was an isopropyl or t-butyl group (**156, 157, 159, 161, 164, 166**). These compounds, like (**148-149**), exhibited weak β-adrenergic antagonist activity (10^{-3} to 10^{-5} M range) and they are non-selective β_1/β_2-antagonists. This group of compounds was equipotent with the 1,4-dihydropyridyl anologues described above.

3) 1-Isoquinolone ring system and R^2 was a t-butyl or cyclohexyl substituent (**255, 256**). These compounds exhibited weak β-adrenergic antagonist activity (10^{-3} to 10^{-4} M range). The t-butyl compound (**255**) exhibited a lower β_1/β_2 selectivity than the (**256**) cyclohexyl analogue.

4) 4-Quinazolone moiety and R^2 was an isopropyl or t-butyl substituent (**259-260**). Compound (**260**) was a less active β-antagonist on both atria and trachea than the corresponding analogue (**255**, R^2= t-Bu). The N-isopropyl analogue (**259**) exhibited a higher β_1/β_2

selectivity (1.57×10^{-2}; a greater selectivity for the β_1-receptor) than the N-t-butyl analogue (**260**) where the β_1/β_2 selectivity ratio was 0.16. This is a general correlation since the β_1/β_2 selectivity is higher for R^2= i-Pr relative to R^2= t-Bu when the heteroaryl group is a 1,2-, 1,6-dihydropyridyl or 1-isoquinolone moiety.

5) Structure-activity correlations A(1-4) suggest an oxygen atom with a free electron-pair may be essential for an efficient β-adrenergic receptor interaction.

B) β-Adrenergic antagonist structure-activity correlations were obtained for selected compounds of general structure (**7**) where the aryl and NHR^2 groups were:

1) Phenyl and 4-phenyl-3-(4,4-dimethyloxazolin-2-yl)-1,4-dihydropyridine (**171**). This compound exhibited weak antagonist activity on both atria and trachea (10^{-4} to 10^{-5} M range).

2) 1-Naphthyl and 4-phenyl (**172**), n-butyl (**176**) or methyl-3-(4,4-dimethyloxazolin-2-yl)-1,4-dihydropyridine (**178**). The test results indicated that the C-4 substituent on the dihydropyridine ring was a determinant of activity with Me > n-Bu > Ph on both atria and trachea. Compounds (**172, 178**) are non-selective β_1/β_2-antagonists (β_1/β_2 ratio of 1). Compound (**176**) had a higher β_2-selectivity (β_1/β_2= 8.72) relative to (**172, 178**). The β_1/β_2-selectivity of these compounds was in the order Me = Ph > n-Bu.

3) 1-Naphthyl and 2-phenyl-3-(4,4-dimethyloxazolin-2-yl)-1,2-dihydropyridine (**174**). This compound exhibited weak β-adrenergic antagonist activity (10^{-3} to 10^{-4} M range).

4) Phenyl (**179**) or 1-Naphthyl (**180**) and 6-n-butyl-3-cyano-1,6-dihydropyridine. These compounds were non-selective antagonists, that were equipotent with the compounds described in B(2). The phenyl compound (**179**) was slightly more active than the 1-naphthyl compound (**180**) on tracheal tissues .

5) Phenyl (**181**) or 1-Napthyl (**182**) and 2-t-butyl-3-cyano-1,2-dihydropyridine. These compounds exhibited weak β-antagonist activity in the 10^{-3} to 10^{-5} M range.

6) The structure-activity correlations described in B(1-5) above suggest an amino hydrogen substituent may be essential for an effective β-adrenergic receptor interaction possibly via H-bonding.

c) β-Adrenergic antagonist structure-activity correlations were obtained for selected compounds of general structure (**7**) where the aryl, configuration of oxypropanolamine side chain and R^2 groups were:

1) 5-quinoline ring system, (R,S) configuration and isopropyl, t-butyl or cyclohexyl (**211, 212, 213**). The pharmacologial results in Table 36 indicate these compounds are very potent and selective β-adrenergic antagonists. Compounds (**211, 212**) are equipotent on right atrium (10^{-7} M range) and left atrium (10^{-8} M range), and 9 fold more potent than propranolol and metoprolol. Compound (**213**) is less potent on atria (10^{-6} M range) and equipotent on trachea (10^{-4} M range) relative to the (**211, 212**) analogues. The test results in Tables 36 and 37 indicated that the activity on atria and the β_1/β_2 selectivity of (**211, 212, 213**) were dependent upon R^2 groups where the potency order was isopropyl > t-butyl > cyclohexyl. This general correlation was also found in A(4).

2) 4-quinoline ring system, (R,S) configuration and isopropyl (**233**). This compound was a markedly less active β-adrenergic antagonist on both atria (10^{-5} M range) and on trachea (10^{-3} M range) than the (**211, 212, 213**) analogues.

3) 2-quinoline ring system, (R,S) configuration and isopropyl or t-butyl (**242a, 242b**). Compound (**242a**) is equipotent to (**242b**) on right atrium (10^{-5} M range) and left atrium (10^{-6} M range). The activity on atria and the β_1/β_2 selectivity ratio for (**242a, 242b**) are much lower than the 4- and 5-positional isomers described in C(1-2).

4) 5-quinoline ring system, (R) configuration and isopropyl or t-butyl (**214, 215**). The test results listed in Table 36 indicate that compounds (**214** and **215**) are ten fold less potent and selective on atria than the racemate (**211, 212**), respectively.

5) 5-quinoline ring system, (S) configuration and isopropyl, t-butyl, cyclohexyl, indolyl-t-butyl, or (S)-α-methylbenzyl (**216-218, 220-221**). The test results in Tables 36, 37 indicate compounds (**216-217**) are equipotent with the racemate (**211, 212**) on atria. The N-isopropyl analogue (S)-(**216**) exhibited the highest β-adrenergic antagonist activity on atria and the highest β_1/β_2 selectivity (1.26×10^{-4}) relative to (**217**) (4.34×10^{-4}), (**218**) (3.22×10^{-3}), (**220**) (5.10×10^{-3}) and (**221**) (see Table 36). Similar results were listed in Table 37 for atria but the β_1/β_2 selectivity ratio are in the order (**216**) < (-[illegible]) < (**218**) (-14.3) < (**221**) (-19.6) which may be due to the high antagonist concentration dose.

6) The structure-activity correlations C(1-3) suggest an oxygen atom with a free electron pair may be essential for an efficient β-adrenergic receptor interaction. Otherwise, the quinoline ring

substituent was more selective for the β_1-receptor than a naphthalene ring which may be due to the negative region generated by nitrogen atom on the second fused ring.

7) The structure-activity correlations C(4-5) suggest that compounds with the (S)-configuration are more active and selective than compounds possessing the (R)-configuration.

D) β-Adrenergic antagonist structure-activity correlations were obtained for compounds of general structure (**7**) where the aryl, configuration of the oxypropanol side chain and NHR^2 groups were:

1) 5-quinoline ring system, (S)-configuration and N^4-benzhydryl-piperazinyl substituent (**222**). The test results in Table 36 indicated that (S)-(**222**) was a weak β-adrenergic antagonist on heart (10^{-5} M range) and on trachea (10^{-4} M range) relative to propranolol (10^{-7} M range). (S)-(**222**) exhibited a marked decrease in β_1/β_2-selectivity (2.0×10^{-1}) relative to (S)-(**216**) (1.26×10^{-4}) or metoprolol (8.5×10^{-3}).

2) These structure-activity correlations suggest that the amino hydrogen substituent may be essential for an effective β-adrenergic receptor interaction as described previously in B(6).

E) β-Adrenergic antagonist structure-activity correlations were obtained for compounds of general structure (**7**) where the aryl, and R^2 groups were a:

1) 2-pyrimidine ring system, and isopropyl or t-butyl (**245a**, **245b**). Compound (**245a**) is equipotent to (**245b**) on atria (10^{-5} M range for right atrium and 10^{-6} M range for left atrium) and less potent than propranolol on both atria and trachea (10^{-7} M range). Compound (**245a**)

possessed a high cardioselectivity with a β_1/β_2 ratio of 2.28 x 10^{-4} (Table 38) or -10.7 (Table 39) relative to (**216**) 1.26 x 10-4 or -6.7 (Table 36 or 37).

2) 2-isoquinoline ring system, and isopropyl, t-butyl or cyclohexyl (**248, 249, 250**). The test results in Tables 38 and 39 indicate that compounds (**248**) and (**249**) are equipotent on both atria ((10^{-6} M range for right atrium and 10^{-7} M range for left atrium) and trachea (10^{-4} M range) and ten fold less active β-adrenergic antagonist activity than (**211**). Compound (**250**) is ten times less active on atria but slightly more active on trachea than (**248**) and (**249**). The β_1-selectivity of these compounds (**248**)=(**249**) (10^{-3}) > (**250**) (10^{-1}) was reduced markedly relative to (**211**) (10^{-4}) (Table 38). In contrast the β_1-selective order (**248**) (5.3) > (**249**) (1.4) > (**250**) (-1.5) may be due to the high antagonist dose.

3) The structure-activity correlations E(1-2) suggest that the free electon-pair on the oxygen atom and an electron negative region on the fused ring may be essential for an effective β-adrenergic receptor interaction.

5.0.0.0.0 EXPERIMENTAL.

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined for solutions in deuterochloroform unless otherwise stated with TMS as internal standard with a Varian EM-360A or Bruker AM-300 spectrometer. Mass spectra were measured with an AEI-MS-50 mass spectrometer. Infrared spectra (potassium bromide unless otherwise noted) were taken on a Nicolet 5DX spectrometer. All of the products gave rise to a single spot on tlc using a solvent system of low, medium and high polarity. Analyses of compounds prepared in this study were in most cases within ± 0.40% of the theoretical values for C, H, and N. If this was not the case accurate mass was acquired. Flash column chromatography was carried out utilizing Merck 60 silica gel. Column chromatography was performed using JT Baker 60-200 mesh silica gel. Preparative thin layer chromatography was performed using Kieselgel silica gel DF-5 (Camag) plates, 1 mm in thickness. Reactions employing NaH were carried out under an atmosphere of nitrogen. Dry nitrogen gas was obtained by passage through concentrated sulfuric acid, solid potassium hydroxide and then anhydrous calcium sulfate.

5.1.0.0.0 SOLVENTS AND REAGENTS.

Tetrahydrofuran and ether were dried by heating at reflux in the presence of sodium metal and benzophenone under a nitrogen atmosphere, followed by distillation immediately prior to use. Epihalohydrins were double-distilled and stored under an atmosphere of nitrogen prior to use. Dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF) were dried by heating at reflux for five hours in the presence of calcium hydride prior to distillation and storage over 4A molecular sieves under a nitrogen atmosphere. 1-Naphthol was recrystallized from ether prior to use.

5.2.0.0.0 PREPARATION OF 4-PHENYL-(144a), 4-n-BUTYL-(144b), AND 4-METHYL-3-(4,4-DIMETHYLOXAZOLIN-2-YL)-1,4-DIHYDROPYRIDINE (144c) (in Scheme 4).

A solution of the organolithium reagent [27 mmol, PhLi in cyclohexane-ether (70:30 v/v), 13.5 mL; n-BuLi in hexane, 10.75 mL; or MeLi in ether, 16 mL] in dry tetrahydrofuran (20 mL) was added dropwise with stirring to a solution of (**134**) (4 g, 22 mmol) in dry tetrahydrofuran (60 mL) under a nitrogen atmosphere at -78 ^{o}C. The reaction mixture was stirred at -78 ^{o}C for an additional 2 h, and then was allowed to return to 25 ^{o}C for 2 h. The reaction mixture was cooled to 0 ^{o}C and cold water (10 mL) was added dropwise. The tetrahydrofuran fraction was separated, and the aqueous layer was extracted with ether (2 x 200 mL). The combined tetrahydrofuran fraction and ethereal extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product contained exclusively (**144a**), whereas the products (**144b** and **144c**) were contaminated by the analogous 1,6-dihydropyridyl isomer. The individual products (**144a-c**) were purified by dissolution in ethyl ether (10 mL). Addition of cold hexane (10-15 mL) yielded crystalline solids which were filtered and recrystallized one more time from the same solvent. Products (**144a**) (93%), (**144b**) (70%) and (**144c**) (80%) prepared in this way were identical (mp, ^{1}H nmr) to literature data[430,412a].

5.3.0.0.0 PREPARATION OF 4-PHENYL-3-(4,4-DIMETHYLOXAZOLIN-2-YL)-1,2-DIHYDROPYRIDINE (170).

A solution of the organolithium reagent [27 mmol, PhLi in cyclohexane-ether (70:30 v/v)] in dry ether (20 mL) was added dropwise with stirring to a solution of (**134**) (4 g, 22 mmol) in dry ethylether (60 mL) under a nitrogen atmosphere at 25 °C and the reaction was allowed to proceed for 2 h. The reaction mixture was cooled to 0 °C and then cold water (10 mL) was added dropwise. The ether fraction was separated, and the aqueous layer was extracted with ether (2 x 200 mL). The combined ethereal extracts were dried (Na_2SO_4) and concentrated *in vacuo* to yield a solid residue. This residue contained a mixture of 1,2- and 1,4-isomers which was separated by fractional crystallization from ether-hexane (1:1 v/v) to afford pure 1,4-dihydropyridine (**144a**) (1 g, 18%), followed by further recrystallization from ether-hexane (3:7 v/v) to yield pure 1,2-isomer (**170**) (3.6 g, 65%), mp 169-170 °C, or by elution from a 3 x 60 cm silica gel column with ether:hexane (6:4 v/v) as the eluant. Removal the solvent from the 200-600 mL eluate afforded the pure 1,2-isomer (**170**). Further elution using ether gave the 1,4-isomer. Compound (**170**) prepared in this way was identical (mp, ^1H nmr) to literature data[430,412a].

5.4.0.0.0 PREPARATION OF 2-t-BUTYL-3-CYANO-1,2-DIHYDROPYRIDYL (154a) AND 6-t-BUTYL-3-CYANO-1,6-DIHYDROPYRIDINE (154b).

A solution of 3-cyanopyridine (**152**) (10 g, 96 mmol) in dry ether (70 mL) was added added dropwise during 2 h to a solution of t-butyllithium in pentane (57.7 mL, 0.11 mol) in dry ether (50 mL) under a nitrogen atmosphere at -78 °C with stirring. After complete addition, the reaction mixture was stirred at -78 °C for an additional 3 h, and then was allowed to return to 25 °C. Cold water (70 mL) was added dropwise and stirring was continued for 0.5 h. Extraction with ether, drying (Na_2SO_4) and removal of the solvent *in vacuo* yielded a pale yellow oil containing a mixture of the 1,2- and 1,6-dihydropyridine. The crude mixture was separated by fractional crystallization from ether-hexane to give pure (**154b**) as a yellow solid (6.4 g, 41.13%), mp 71 °C (lit.[444] as an oil). Evaporation of the ether-hexane mother liquor gave a mixture of 1,2- and 1,6-dihydropyridines (7.4 g) that were separated by elution from a 3 x 60 cm silica gel column with ether:hexane (4:6 v/v) as the eluant. Removal the solvent from the 200-600 mL eluate afforded the pure 1,2-isomer (**154a**) and from the 650-1000 mL eluate afforded the 1,4-isomer (**154b**). Removal of the solvent gave (**154a**) (4 g, 25.70%) as an oil and (**154b**) as solid (3 g, 19.28%), mp 71 °C. Compounds (**154a,b**) prepared in this way were identical (^1H nmr) to literature data,[444] except for the 1,6-dihydropyridine which was isolated as a yellow solid.

5.5.0.0.0 PREPARATION OF 2-n-BUTYL-3-CYANO-1,2-(154c) and 1,6-DIHYDROPYRIDINE (154d).

Compounds (**154c,d**) were prepared using a procedure similar to that described for (**154a,b**). The residue obtained was separated by elution from a 3 x 60 cm silica gel column with ether:hexane (2:8 v/v) as the eluant. Removal of the solvent from the 200-600 mL eluate afforded pure 1,2-isomer (**154c**) as a yellow oil in 20% yield. Further elution using increasing amounts of ether (ether:hexane = 1:1 v/v) afforded the 1,6-isomer (**154d**) as a yellow oil in 58% yield.. Compounds (**154c,d**) prepared in this way were identical (mp, ^{1}H nmr) to literature data[444].

5.6.0.0.0 GENERAL METHOD FOR THE PREPARATION OF 1-[ARYL(OR 1-NAPHTHYL)OXY]-2,3-EPOXYPROPANES (169a,b).

A solution of the appropriate phenol (4 g, 42.5 mmol), or 1-naphthol (6.12 g, 42.5 mmol) in epichlorohydrin (0.25 mmol, 20 mL) was treated with 7 drops of piperidine and heated at reflux for 6 h. Unreacted epibromohydrin was removed under vacuum. Toluene (150 mL) was added to the residue. This procedure was repeated a second time, and the solvent removed *in vacuo*. The residue was stirred with tetrahydrofuran (100 mL) and 1N NaOH (42.5 mL) for 15 min at 60 °C and for 1 h at 25 °C. The solvent was removed *in vacuo* and the resulting suspension was extracted with methylene chloride (3 x 150 mL), dried (Na_2SO_4) and concentrated to yield (**169a**) as an oil (3.82 g, 60%), R_f= 0.85 with ether as development solvent which could be used without further purification or (**169b**) as an oil (5.52 g, 65%), R_f= 0.55 using ether-hexane (1:1 v/v) as development solvent which could be purified by distillation (0.3 mm Hg/140 °C). Compounds (**169a,b**) prepared in this way were identical (mp, ^{1}H nmr) to literature data[445.446].

5.7.0.0.0 GENERAL METHOD FOR THE SYNTHESIS OF 1-{1-[4-PHENYL-3-(4,4-DIMETHYLOXAZOLIN-2-YL)-1,4-DIHYDROPYRIDYL]}-3-t-BUTYL(or ISOPROPYL)AMINO-2-PROPANOLS (146-147).

METHOD A.

A solution of phenyllithium in cyclohexane-ethyl ether (70:30 v/v) (3.1 mmol, 1.56 mL) in dry tetrahydrofuran (THF) (5 mL) was added dropwise with stirring to a solution of **(134)** (0.5 g, 2.8 mmol) in dry THF (50 mL) under a nitrogen atmosphere at -78 °C. The reaction mixture was stirred for 2 h at -78 °C, epichlorohydrin (2.8 mmol, 0.23 mL) in dry THF (2 mL) was added dropwise and the mixture was stirred at -78 °C for 1 h. The reaction mixture was allowed to warm to 25 °C, stirred at 25 °C for an additional 2 h, and cold 1 N NaOH (3 mL) was added. The reaction mixture was then stirred for 10 min at 60 °C and 30 min at 25 °C. The solvent was removed *in vacuo* and the resulting suspension was extracted with ether (3 x 150 mL). The organic layer was dried (Na_2SO_4) and evaporated to give **(145)** as an oil which could be used without further purification. Subsequently, the mixture of **(145)** and t-butylamine (14 mmol, 1.41 mL) in 2-propanol (5 mL) was stirred for 36 hr at 25 °C. The solvent and excess amine were evaporated *in vacuo*. The crude product was purified on silica gel G plates using ether-methanol (70:30 v/v) as development solvent. Extraction of the band having R_f 0.48 with methanol yielded **(146)** as a light yellow solid (0.48 g, 45%), mp 63-65 °C.

Compound **(147)** was prepared using the same procedure described for the synthesis of **(146)**. The crude product was purified by elution from a 2.5 x 30 cm silica column with ethyl acetate-methanol (9:1 v/v) as eluant. Removal of the solvent from the 200-600 mL eluate afforded

(**147**) as a light yellow solid (0.34 g, 33%), mp 73-75 ^{o}C. The physical, ir and ^{1}H nmr spectral data for (**146-147**) are listed in Tables 1 and 2.

METHOD B.

NaH (0.1 g, 3.36 mmol, 80% suspension in mineral oil) was washed with dry hexane and dried under a nitrogen atmosphere prior to addition of DMSO (5 mL). A solution of (**144a**) (0.72 g, 2.8 mmol), prepared using the method described in section 4.2.0.0.0, in DMSO (30 mL) was added dropwise under a nitrogen atmosphere at 0^{o}C. After completion of the addition, the mixture was stirred at 50 ^{o}C for 30 min. and at room temperature until no further evolution of hydrogen gas was observed (1.5 h). A solution of epibromohydrin (**205**) (0.24 mL, 2.8 mmol) in DMSO (2 mL) was then added during a period of 10 min. After stirring for 12 h at 25 ^{o}C, the excess DMSO was partially removed under reduced pressure. The mixture was poured into ice-water (5 mL), extracted with ether (200 x 3 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield (**145**) as an oil which was used without further purification. t-Butylamine (14 mmol, 1.41 mL) or isopropylamine (14 mmol, 1.2 mL) in 2-propanol (5 mL) was added and the reaction mixture was stirred for 36-48 hr at 25 ^{o}C. The solvent and excess amine were evaporated *in vacuo* to afford (**146**) (0.7 g, 70%) and (**147**) (0.7 g, 68%) as a light yellow solids, respectively. The physical, ir and ^{1}H nmr spectral data for (**146-147**) were the same as those described in method A.

5.7.1.0.0 SYNTHESIS OF 1-{1-[4-n-BUTYL-3-(4,4-DIMETHYLOXAZOLIN-2-YL)-1,4-DIHYDROPYRIDYL]}-3-t-BUTYL(OR ISOPROPYL)AMINO-2-PROPANOLS (148-149).

METHOD A.

A solution of n-butyllithium in hexane (3.1 mmol, 1.24 mL) in dry THF (5 mL) was added dropwise with stirring to a solution of (**134**) (0.5 g, 2.8 mmol) in dry THF (40 mL) under a nitrogen atmosphere at -78 °C. The reaction mixture was stirred for 2 h, epichlorohydrin (2.8 mmol, 0.23 mL) in dry THF (2 mL) was added dropwise and the mixture was stirred at -78 °C for 1 h. The reaction mixture was allowed to warm to 25 °C, stirred at 25 °C for an additional 2 h, and cold 1 N NaOH (3 mL) was added. The reaction mixture was then stirred for 10 min at 60 °C and 30 min at 25 °C. The solvent was removed in vacuo and the resulting suspension was extracted with ether (3 x 150 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo* to give (**145**) containing a trace of the analogous 1,6-dihydropyridyl isomer. t-Butylamine (14 mmol, 1.41 mL) in 2-propanol (5 mL) was added and the reaction was allowed to proceed with stirring for 36 h at 25 °C. The solvent and excess amine were evaporated *in vacuo*. The crude product was purified on silica gel G tlc plates using ether-methanol (70:30 v/v) as development solvent. Extraction of the bright yellow band having R_f 0.5 with methanol yielded (**148**) as an oil (0.35 g, 35%). Compound (**149**), which was prepared using a similar procedure as (**148**), was obtained as an oil (0.3 g, 30%). The physical, ir and ^1H nmr spectral data for (**148-149**) are provided in Tables 1 and 2.

METHOD B.

Compounds (**148-149**) were prepared using method B as described for the preparation of (**146-147**). The crude product was purified on silica gel G plates using ether-methanol (70:30 v/v) as development solvent as described in method A to yield (**148**) (63%) and (**149**) (60%), respectively.

5.7.2.0.0 SYNTHESIS OF 1-{1-[4-METHYL-3-(4,4-DIMETHYLOXAZOLIN-2-YL)-1,4-DIHYDROPYRIDYL]}-3-t-BUTYL(or ISOPROPYL)AMINO-2-PROPANOLS (150-151).

Method A.

Compounds (**150-151**) were prepared as described in method A for the synthesis of (**148-149**). The crude products were contaminated by traces of the analogous 1,6-dihydropyridyl isomer which exhibited a more colorful band and moved faster on a tlc plate than the 1,4-isomer. The individual products were purified on silica gel G tlc plates using ether-methanol (70:30 v/v) as development solvent. Extraction of the bright yellow band having R_f 0.46 with methanol yielded (**150**) as an oil (0.34 g, 38%), and the band having R_f 0.45 with methanol yielded (**151**) as an oil (0.3 g, 36%). The physical, ir and ^1H nmr spectral data for (**150-151**) are listed in Tables 1 and 2.

Method B.

Compounds (**150-151**) were prepared as described in method B for the synthesis of (**146-147**). The residual oil obtained was purified on silica gel G tlc plates using ether-methanol (70:30 v/v) as development solvent to provide the same products obtained in method A (0.58 g, 65% yield, **150**) and (0.53, 62% yield, **151**).

5.8.0.0.0 GENERAL METHOD FOR THE SYNTHESIS OF 1-{1-[6-n-BUTYL-3-CYANO-1,6-DIHYDROPYRIDYL]}-3-ISOPROPYLAMINO-2-PROPANOL (156) AND 1-{1-[2-n-BUTYL-3-CYANO-1,2-DIHYDROPYRIDYL]}-3-ISOPROPYLAMINO-2-PROPANOL (159).

METHOD A.

A solution of 3-cyanopyridine (**152**) (1 g, 9.6 mmol) in dry ether (20 mL) was added dropwise during 0.5 h to a solution of n-butyllithium in pentane (5.8 mL, 0.01 mol) in dry ether (30 mL) under a nitrogen atmosphere at -78 °C with stirring. After complete addition, the reaction mixture was stirred at -78 °C for an additional 2 h. Epibromohydrin (9.6 mmol, 0.82 mL) in dry ether (2 mL) was added dropwise and the reaction mixture was stirred at -78 °C for 1.5 h. The reaction mixture was allowed to warm to 25 °C, stirred at 25 °C for an additional 1 h, and cold 1 N NaOH (9.6 mL) was added. The reaction mixture was then stirred for 15 min at 60 °C and for 40 min at 25 °C. The solvent was removed *in vacuo* and the resulting suspension was extracted with ether (3 x 150 mL). The organic layer was dried (Na_2SO_4) and evaporated to give a mixture of (**155a,b**). The residual oil (**155a,b**) was used without further purification by mixing with isopropylamine (57.6 mmol, 4.9 mL) in 2-propanol (10 mL). The reaction mixture was stirred for 36 h at 25 °C. The solvent and excess amine were evaporated *in vacuo*. The crude product was purified on silica gel G plates using ether-methanol (70:30 v/v) as development solvent.

Extraction the band having R_f 0.45 with methanol yielded (**156**) as an oil (1.0 g, 40%), and the band having R_f 0.5 with methanol yielded (**159**) as an oil (0.34 g, 13%). The physical, ir and ^1H nmr spectral data for (**156**) and (**159**) are summarized in Tables 3 and 4.

METHOD B.

NaH (0.14 g, 3.3 mmol, 60% suspension in mineral oil) was washed with dry hexane and dried under a nitrogen atmosphere prior to addition of DMSO (5 mL). A solution of pure (**154a**) or (**154b**) prepared in section 4.4.0.0.0 (0.5 g, 3.0 mmol) in DMSO (30 mL) was added dropwise under a nitrogen atmosphere at 0 °C. After completion of the addition, the mixture was stirred at 50 °C for 30 min and at room temperature until no further evolution of hydrogen gas was evident (1 h). A solution of epibromohydrin (**205**) (0.26 mL, 3.0 mmol) in DMSO (2 mL) was then added during a period of 10 min. After stirring for 8 h at 25 °C, the excess DMSO was partially removed under reduced pressure. The mixture was poured into ice-water (5 mL), extracted with ether (2 x 200 mL), dried (Na_2SO_4), concentrated *in vacuo* to yield (**155a**) or (**155b**). Subsequently, a mixture of (**155a**) or (**155b**) and isopropylamine (14 mmol, 1.41 mL) in 2-propanol (5 mL) was stirred for 36-48 h at 25 °C. The solvent and excess amine were evaporated *in vacuo* to afford (**156**) (0.58 g, 70%) and (**159**) (0.54 g, 65%), respectively. The physical, ir and ^1H nmr spectral data for (**146-147**) were identical to that described in method A.

5.8.1.0.0 SYNTHESIS OF 1-{1-[6-n-BUTYL-3-CYANO-1,6-DIHYDROPYRIDYL]}-3-t-BUTYLYLAMINO-2-PROPANOL (157) 1-{1-[2-n-BUTYL-3-CYANO-1,2-DIHYDROPYRIDYL]}-3-t-BUTYLAMINO-2-PROPANOL (160).

METHOD A.

Compounds **(157)** and **(160)** were prepared using the procedure described for the synthesis of **(156)** and **(159)**. A mixture of (**155a** or **b**) (1.6 g, 7.6 mmol) with t-butylamine (57.6 mmol, 6.0 mL) in 2-propanol (15 mL) was stirred for 48 h at 25 °C. The solvent and excess amine were evaporated *in vacuo*. The crude product was purified on silica gel G plates using ether-methanol (70:30 v/v) as development solvent. Extraction of the band having R_f 0.46 with methanol yielded **(157)** as an oil (1.17 g, 42%); and the band having R_f 0.52 with methanol yielded **(160)** as an oil (0.44 g, 16%). The physical, ir and ^{1}H nmr spectral data for **(157)** and **(160)** are presented in Tables 3 and 4.

METHOD B.

Compounds **(157)** and **(160)** were prepared by method B using the procedure described for the synthesis of **(156)** and **(159)**. A mixture of (**155a** or **155b**) (0.49 g, 2.4 mmol) and t-butylamine (14 mmol, 1.5 mL) in 2-propanol (5 mL) was stirred for 48 h at 25 °C. The solvent and excess amine were evaporated *in vacuo* to give **(157)** (0.63 g, 73%) and **(160)** (0.6 g, 70%) as an oil. Compound **(157)** is comprised of two different diastereomers (RR=SS and RS=SR) which were separated on silica gel G tlc plates with ether:methanol (7:3 v/v) as development solvent using the multiple development tlc technique (repeated three times). Extraction of the top part of the band having R_f 0.5 with methanol afforded a pure diastereomer (**158**) (0.22 g, 25%) as an oil. Compounds (**157**, and **160**) exhibited the same physical, ir and ^{1}H nmr spectral data as described earlier in method A . The physical, ir and ^{1}H nmr spectral data for (**158**) are presented in Tables 3 and 4.

5.8.2.0.0 SYNTHESIS OF 1-{1-[6-t-BUTYL-3-CYANO-1,6-DIHYDROPYRIDYL]}-3-ISOPROPYLAMINO-2-PROPANOLS (161-164) and 1-{1-[2-t-BUTYL-3-CYANO-1,2-DIHYDROPYRIDYL]}-3-ISOPROPYLAMINO-2-PROPANOL (166).

Compounds (**161-164**) were prepared by method B as described earlier for the synthesis of (**156**) and (**159**). A mixture of (**155c**) (0.51 g, 2.49 mmol) and isopropylamine (14 mmol, 1.41 mL) in 2-propanol (5 mL) was stirred for 36 h at 25 ^{o}C. The solvent and excess amine were evaporated *in vacuo*. The residual oil obtained contained two different diastereomers (RR=SS and RS=SR) which were separated on silica gel G tlc plates using ether:methanol (7:3 v/v) as development solvent using the multiple development TLC technique (repeated two times). Extraction the top part of band having R_f 0.5-0.55 with methanol afforded a partially pure diastereomer mixture with a 2:1 ratio (**161**) (0.3 g, 33%) as an oil, and the lower band having R_f 0.4-0.5 with methanol afforded a partially pure diastereomer mixture with a 1:2 ratio (**162**) (0.27 g, 30%) as an oil. Compound (**161**) was further separated on silica gel G plates with ether:methanol (8:2 v/v) as development solvent using the multiple development TLC technique (repeated three times). Extraction of the top part of band having R_f 0.55-0.6 afforded a pure single diastereomer (**163**) (0.2 g, 22%) as an oil. Similarly, (**164**) was separated using the same solvent as described for (**163**). Extraction of the lower part of band having R_f 0.46-0.50 afforded a pure single diastereomer (**164**) (0.23 g, 27.5%) as an oil. The physical, ir and ^{1}H nmr spectral data for (**161-164**) are summarized in Tables 3 and 4.

Compound (**166**) was prepared using the procedure described for the preparation of (**161-164**). A mixture of (**155d**) (0.49 g, 2.4 mmol) and t-butylamine (14 mmol, 1.5 mL) in 2-propanol (5 mL) were stirred for 48 h at 25 °C and the solvent was removed *in vacuo*. The residue was purified on silica gel G tlc plates with ether:methanol (7:3 v/v) as development solvent using the multiple development tlc technique (repeated three times). Extraction of the band having R_f 0.5 afforded (**166**) (0.64 g, 78%) as an oil .

5.8.3.0.0 SYNTHESIS OF 1-{1-[6-t-BUTYL-3-CYANO-1,6-DIHYDROPYRIDYL]}-3-t-BUTYLAMINO-2-PROPANOL (165) AND 1-{1-[2-n-BUTYL-3-CYANO-1,2-DIHYDROPYRIDYL]}-3-t-BUTYLAMINO-2-PROPANOL (167).

Compounds (**165** and **167**) were prepared by method B using the procedure described for the synthesis of (**161-164**). A mixture of (**155c**) or (**155d**) (0.53 g, 2.55 mmol) and t-butylamine (14 mmol, 1.5 mL) in 2-propanol (5 mL) were stirred for 48 h at 25 °C and the solvent was removed *in vacuo*. The residual oil obtained from the reaction with (**155c**) was purified on silica gel G tlc plates using ether:ethanol (7:3 v/v) as development solvent using the multiple development TLC technique (repeated three times). Extraction of the band having R_f 0.5 with methanol afforded (**167**) (0.69 g,80%) as a yellow solid, mp 82-84 °C. The residual oil obtained from the reaction employing (**155d**) was purified using the same solvent as described for (**167**). Extraction of the band having R_f 0.46-0.5 afforded a pure single diastereomer (**165**) (0.34 g, 40%) as a white solid, mp 117 °C.

5.9.0.0.0 GENERAL METHOD FOR THE SYNTHESIS OF 1-ARYLOXY-3-{1-[2-(or 4-)ALKYL(OR PHENYL)-3-(4,4-DIMETHYLOXAZOLIN-2-YL)-1,2-(or 1,4)-DIHYDROPYRIDYL]}-2-PROPANOLS (171-178).

The general method used for the synthesis of (**171-178**) (see Scheme 8) involved the reaction of pure 1,2- or 1,4-dihydropyridyl compound (**170** or **144**) (prepared in section 4.3.0.0.0 and 4.2.0.0.0) with the aryloxyepoxypropane (**169**) (prepared in section 4.6.0.0.0) in the presence of NaH in DMSO.

5.9.1.0.0 SYNTHESIS OF 1-PHENOXY-3-{1-[2-(or 4-)ALKYL(ARYL)-3-(4,4-DIMETHYLOXAZOLIN-2-YL)-1,2-(or 1,4-)DIHYDROPYRIDYL]}-2-PROPANOLS (171,173,175,177).

NaH (0.175 g, 4.3 mmol, 60% suspension in mineral oil) was added dropwise to a solution of [**144 a,b** or **c**) 4-(phenyl, butyl or methyl)-3-(4,4-dimethyloxazolin-2-yl)-1,4 dihydropyridines (0.9 g, 0.8 g or 0.7 g; 3.64 mmol] in DMSO (20 mL) under a nitrogen atmosphere at 0 °C. This mixture was stirred at 50 °C for 30 min. and then at room temperature until no further evolution of hydrogen gas was observed (1.5 h). A solution of the 1-aryloxy-2,3-epoxypropane (**169a**, 0.54 g, 3.64 mmol) in DMSO (12 mL) was then added during a period of 10 min. After stirring for 7 h at 25 °C, the excess DMSO was partially removed under reduced pressure. The mixture was poured into ice-water (5 mL), extracted with ether (200 x 3 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residual oil obtained from the (**144 a**) reaction was purified on silica gel G plates with ether:hexane (7:3 v/v) as development solvent. Extraction of the bright yellow band having R_f 0.5 with methanol afforded (**171**) (1.21 g, 83%) as a yellow foam-like solid with mp 55 °C. The residual oil obtained from the (**144b**) reaction was purified on silica gel G plates using ether:hexane (7:3 v/v) as development solvent. Extraction of the band having R_f 0.52 with methanol afforded (**175**) (1.09 g, 79%) as a yellow oil. The residual oil obtained from the (**144c**) reaction was purified on silica gel G plates with ether:hexane (7:3 v/v) as development solvent. Extraction of the band having R_f 0.48 with methanol afforded (**177**) (1 g, 81%) as a yellow oil. Similarly, the reaction of (**170**) (0.5 g, 1.96 mmol) with (**169a**) (0.29 g, 1.96 mmol) in the presence of NaH (0.08 g, 2.36 mmol, 60% suspension in mineral oil) gave a residue which was purified on silica gel G plates using ether:hexane (8:2 v/v) as development solvent. Extraction of the yellow color band having R_f 0.55 with methanol afforded (**173**) (0.64 g, 82%) as a yellow foam-like solid, mp 45 °C.

5.9.2.0.0 SYNTHESIS OF 1-(1-NAPTHOXY)-3-{1-[2-(or 4-)ALKYL (ARYL)-3-(4,4-DIMETHYLOXAZOLIN-2-YL)-1,2-(or 1,4-) DIHYDROPYRIDYL]}-2-PROPANOLS (172,174,176,178).

Compounds (**172,174,176,178**) were prepared using the procedure outlined in section 5.1.0.0.0. Reaction of 4-(phenyl, butyl, or methyl)-3-(4,4-dimethyloxazolin-2-yl)-1,4-dihydropyridine [**144 (a, b** or **c)** 0.63 g, 0.58 g, 0.48 g; 2.5 mmol] with 1-napthyloxy-2,3-epoxypropane (**169b** 0.5 g, 2.5 mmol) was carried out in the presence of NaH (0.12 g, 3 mmol, 60% suspention in mineral oil) in DMSO (20 mL) under a nitrogen atmosphere at 25 °C for 10 h. The crude product from the (**144a**) reaction crystallized from ether:hexane upon standing in the refrigerator to give (**172**) (0.96 g, 85%) as a yellow solid, mp 70 °C. The crude oil from the (**144b**) reaction was purified on silica gel G plates using ether:hexane (8:2 v/v) as development solvent. Extraction of the yellow band having R_f 0.62 with methanol afforded (**176**) (0.82 g, 80%) as a yellow foam-like solid, mp 45 °C. The crude oil from the (**144c**) reaction was purified on silica gel G plates using ether:hexane (8:2 v/v) as development solvent. Extraction of the yellow band having R_f 0.58 with methanol afforded (**178**) (0.8 g, 83%) as a yellow oil. Similarly, the reaction of (**170**) (0.5 g, 1.96 mmol) with (**169b**) (0.39 g, 1.96 mmol) in the presence of NaH (0.08 g, 2.36 mmol, 60% suspension in mineral oil) gave a residue which was purified on silica gel G plates using ether:hexane (8:2 v/v) as development solvent. Extraction of the yellow band having R_f 0.63 with methanol afforded (**174**) (0.37 g, 42%) as a yellow oil. Alternatively, the product was purified by elution from a 2.5 x 30 cm silica column using ether:hexane (7:3 v/v) as eluant. Removal of the solvent from the 200-600 mL eluate afforded (**174**) as an yellow oil (0.35 g, 40%).

5.9.3.0.0 GENERAL METHOD FOR THE SYNTHESIS OF 1-ARYLOXY-3-{1-[2-(or 6-)ALKYL-3-CYANO-1,2-(or 1,6-)DIHYDROPYRIDYL]}-2-PROPANOLS (179-184).

The general method used for the synthesis of (**179-184**) (see Scheme 9) involved the reaction of the intermediate N-organolithium compound (**153**) with the aryloxyepoxypropane (**169**) in ether using method A or the reaction of a pure 1,2- or 1,6-dihydropyridyl compound

(**154a,b; or 154c,d**) with the aryloxyepoxypropane (**169**) in the presence of NaH in DMSO using method B.

5.9.4.0.0 SYNTHESIS OF 1-PHENOXY-3-{1-[6-n-BUTYL-3-CYANO-1,6-DIHYDROPYRIDYL]}-2-PROPANOL (179) AND 1-(1-NAPTHOXY)-3-{1-[6-n-BUTYL-3-CYANO-1,6-DIHYDROPYRIDYL]}-2-PROPANOL (180).

METHOD A.

A solution of 3-cyanopyridine (**152**) (1 g, 9.6 mmol) in dry ether (20 mL) was added added dropwise during 0.5 h to a solution of n-butyllithium in pentane (5.8 mL, 0.01 mol) in dry ether (30 mL) under a nitrogen atmosphere at -78 °C with stirring. This solution was stirred at -78 °C for an additional 2 h, 1-phenoxy-2,3-epoxypropane (**169a**, 1.43 g, 9.6 mmol) in dry ether (20 mL) was added dropwise and the reaction was allowed to proceed at -78 °C for 1.5 h. The reaction mixture was allowed to warm to 25 °C, stirred at 25 °C for an additional 10 h, and then cold water (5 mL) was added. The solvent was removed *in vacuo* and the resulting suspension was extracted with ether (3 x 150 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated to give a mixture of 1,2- and 1,6-diastereomers which were separated on silica gel G plates with ether:hexane (7:3 v/v) as development solvent. Extraction of the yellow band having R_f 0.6 with methanol afforded the 1,2-isomer that decomposed upon standing at 25 °C. Extraction of the band having R_f 0.52 with methanol gave (**179**) (1.19 g, 40%) as an oil. Similarly, the reaction of the intermediate (**153**) with 1-napthoxy-2,3-

epoxypropane (**169b**, 1.92 g, 9.6 mmol) gave a crude product which was purified on silica gel G plates using ether:hexane (7:3 v/v) as development solvent. Extraction of the yellow band having R_f 0.62 with methanol afforded the 1,2-isomer that also decomposed upon standing at 25 °C. Extraction of the band having R_f 0.60 with methanol gave (**180**) (1.46 g, 42%) as a light yellow solid, mp 95 °C .

METHOD B.

Compound (**179**) was prepared by method B using the procedure described for the preparation of (**156**) and (**159**). NaH (0.46 g, 11.52 mmol, 60% suspension in mineral oil) was washed with dry hexane and dried under a nitrogen atmosphere prior to adding DMSO (5 mL). A solution of pure (**154d**, 1.55 g, 9.6 mmol, prepared in section 4.5.0.0.0) in DMSO (30 mL) was added dropwise under a nitrogen atmosphere at 0 °C. The mixture was stirred at 60 °C for 30 min and then at room temperature until no further evolution of hydrogen gas was evident (2.5 h). A solution of 1-phenoxy-2,3-epoxypropane (**169a**, 1.43 g, 9.6 mmol) in DMSO (25 mL) was then added during a period of 30 min. After stirring for 8 h at 25 °C, the excess DMSO was partially removed under reduced pressure. The mixture was poured into ice-water (10 mL), extracted with ether (3 x 200 mL), dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude oil obtained was purified, as described in method A, to afford (**179**) (2.4 g, 80%).

5.9.5.0.0 SYNTHESIS OF 1-PHENOXY-3-(1-[2-(or 6-)-t-BUTYL-3-CYANO]-1,2-(OR 1,6-)-DIHYDROPYRIDYL)-2-PROPANOLS (181,183) AND 1-(1-NAPTHOXY)-3-(1-[2-(or 6-)-t-BUTYL-3-CYANO]-1,2-(or 1,6-)-DIHYDROPYRIDYL)-2-PROPANOLS (182,184).

Due to the low product yield using method A, compounds (**181-184**) were prepared by method B using the procedure described for the synthesis of (**179**). The reaction of **154a** (0.5 g, 3.0 mmol) with **169a** or **169b** (0.45 g or 0.6 g; 3.0 mmol) was carried out in the presence of NaH under a nitrogen atmosphere at 25 °C for 8 h. The oil obtained from reaction of (**154a**) with (**169a**) was purified on silica gel G plates using ether:hexane (7:3 v/v) as development solvent. Extraction of the band having R_f 0.55 with methanol afforded (**181**) (0.73 g, 78%) as an oil. Extraction of the band having R_f 0.65 (ether:hexane 7:3 v/v) with methanol, obtained by tlc purification of the crude oil obtained from reaction of (**154a**) with (**169b**), afforded (**182**) (1.0 g, 82%) as an oil. Similarly, the reaction of **154b** (0.5g, 3.0 mmol) with **169a** or **169b** (0.45g or 0.6 g; 3.0 mmol) was carried out in the presence of NaH under a nitrogen atmosphere at 25 °C for 7 h. The crude oil obtained from reaction of (**154a**) with (**169a**) was purified on silica gel G plates using ether:hexane (7:3 v/v) as development solvent. Extraction of the band having R_f 0.53 with methanol afforded (**183**) (0.7 g, 76%) as an oil. Extraction of the band having R_f 0.62 (ether:hexane 7:3 v/v) with methanol, obtained by tlc purification of the crude oil obtained from reaction of (**154b**) with (**169b**), afforded (**184**) (0.86 g, 80%) as an oil.

6.0.0.0.0 SYNTHESIS OF ETHYLIMINONICOTINATE (185).

Sodium methoxide (0.25 g, 4.8 mmol) was added to a flask containing nicotinonitrile (**138**) (5 g, 48 mmol) in absolute ethanol (50 mL). The reaction mixture was stirred at room temperature for three days and glacial acetic acid (0.27 mL, 4.8 mmol) was added. The mixture was stirred for an additional 30 min. The solvent was evaporated *in vacuo* to give an oil, which was contaminated with unreacted nicotinonitrile (**138**), was separated by distillation. Collection of the fraction (bp 60 °C / 20 mm Hg) gave ethyliminonicotinate (**185**) (5.0 g, 70%) as an oil. ^{1}H nmr ($CDCl_3$) δ: 1.45 (t, J= 6.9 Hz, 3H, $O\text{-}CH_2\text{-}\underline{CH_3}$); 4.35 (quartet, J= 6.9 Hz, 2H, $O\text{-}\underline{CH_2}\text{-}CH_3$); 7.38 (d, $J_{4,5}$= 8.1 Hz of d, $J_{5,6}$= 4.76 Hz, 1H, pyridyl H-5); 7.9 (br s, 1H, imidate NH, exchanges with deuterium oxide); 8.12 (d, $J_{4,5}$= 8.1 Hz of d, $J_{4,6}$= 1.9 Hz, 1H, pyridyl H-4); 8.72 (d, $J_{5,6}$= 4.76 Hz of d, $J_{4,6}$= 1.9 Hz, 1H, pyridyl H-6); 9.08 (s, 1H, pyridyl H-2); ir (KBr) (cm^{-1}): 1638 (C=N) and 3287 (NH).

6.1.0.0.0 SYNTHESIS OF 2-(3-PYRIDINYL)-4-(S)-METHOXYMETHYL-5-(S)-PHENYL-2-OXAZOLINE (140).

A mixture of ethyliminonicotinate (**185**) (2.0 g, 13.3 mmol), (+)-(1S,2S)-2-amino-1-phenyl-1,3-propanediol (**186**) (2.22 g, 13.3 mmol) and triethylamine (13.3 mmol, 1.85 mL) in dry 1,2-dichloroethane (40 mL) was heated at reflux for 16 h and the solvent was removed *in vacuo*. The resulting oil crystallized from ether:hexane on standing in a cooling bath at 0 °C to give 2-(3-pyridyl)-4-(S)-hydroxymethyl-5-(S)-phenyl-2-oxazoline (**187**) (3 g, 90%) as a solid, 125-126 °C, optical rotation $[\alpha]_D^{23}$= -34.36 (c 0.40, $CHCl_3$), R_f 0.48 with ether:ethanol (7:3 v/v) as development solvent. ^{1}H nmr ($CDCl_3$) δ: 3.82 (m, 1H, $CH_2O\underline{H}$, exchanges with deuterium oxide); 3.88 (d, J_{vic}= 3.51 Hz of d, J_{gem}= 11.7 Hz, 1H, oxazolinyl C-4 $C\underline{H}H^{1}OH$); 4.24 (d, J_{vic}= 3.51 Hz of d, J_{gem}= 11.7 Hz, 1H, oxazolinyl C-4 $CH\underline{H}^{1}OH$); 4.33 (m, 1H, oxazolinyl H-4 proton); 5.56 (d, J= 8.0 Hz, oxazolinyl H-5); 7.35 (m, 1H, pyridyl H-5); 7.42 (m, 5H, phenyl hydrogens); 8.22 (d, $J_{4,5}$= 7.7 Hz of d, $J_{4,6}$= 1.6 Hz of d, $J_{2,4}$= 1.6 Hz, 1H, pyridyl H-4); 8.72 (d, $J_{5,6}$= 5.3 Hz of d, $J_{4,6}$= 1.6 Hz, 1H, pyridyl H-6); 9.26 (d, $J_{2,4}$= 1.6 Hz, 1H, pyridyl H-2). Subsequently, 2-(3-pyridyl)-4-(S)-hydroxymethyl-5-(S)-phenyl-2-oxazoline (**187**) (3 g, 11.8 mmol) in THF (60 mL) was added dropwise to a stirred heterogeneous suspension of sodium hydride (0.56 g, 14.1 mmol, 80% suspension in mineral oil where the mineral oil had been removed by washing with 15 mL of dry hexane) prior to adding THF (15 mL) at a rate to maintain a mild evolution of hydrogen gas at 25 °C under a nitrogen atmosphere. When the addition was complete, the mixture was heated at 60 °C for 20 min, cooled to 25 °C and a solution of methyl iodide (11.8 mmol, 0.73 mL) in THF (5 mL) was added dropwise. The reaction mixture was stirred for 2 h at 25 °C and slowly poured into ice-water (50 mL) prior to extraction with ether (2 x 200 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give (**140**) (3 g, 95%) as an oil having optical ratation $[\alpha]_D^{23}$= +44.16 (c 0.60, $CHCl_3$). ^1H nmr ($CDCl_3$) δ: 3.5 (s, 3H, oxazolinyl C-4 $CH_2OC\underline{H}_3$); 3.68 (d, J_{vic}= 5.8 Hz of d, J_{gem}= 9.8 Hz, 1H, oxazolinyl C-4 $C\underline{H}H^{1}OCH_3$); 3.77 (d, J_{vic}= 4.1 Hz of d, J_{gem}= 9.8 Hz, 1H, oxazolinyl C-4 $CH\underline{H}^{1}OCH_3$); 4.39 (m, 1H, oxazolinyl H-4); 5.56 (d, J= 7 Hz, 1H, oxazolinyl H-5); 7.42 (m, 5H, phenyl hydrogens); 8.35 (d, $J_{4,5}$= 7.9 Hz of d, $J_{4,6}$= 1.6 Hz of d, $J_{2,4}$= 1.6 Hz, 1H, pyridyl H-4); 8.78 (d, $J_{5,6}$= 4.8 Hz of d, $J_{4,6}$= 1.6 Hz, 1H, pyridyl H-6); 9.30 (d, $J_{2,4}$= 1.6 Hz, 1H, H-2); ir (KBr): 1654 (oxazolinyl C=N) cm^{-1}; microanalysis for (**140**)

$C_{16}H_{16}N_2O_2$: found (calcd) C, 71.26 (71.62) ; H, 5.92 (6.01); N, 10.31 (10.44).

7.0.0.0.0 GENERAL PROCEDURE FOR THE SYNTHESIS OF (2R,2S), (2R), OR (2S)-1-(QUINOL-5-YLOXY)-2,3-EPOXYPROPANES (208, 209, 210).

To a dry 150 mL three neck flask, NaH (0.54 g, 17.9 mmol, 80% suspension in mineral oil) that had been washed with dry hexane and dried under a stream of nitrogen gas for 1 h, DMF (6 mL) was added. A solution of 5-hydroxyquinoline (**204**) (2 g, 13.77 mmol) in DMF (25 mL) was added dropwise over 1 hr, with stirring at ice-bath temperature. The reaction mixture was then stirred at room temperature for 3 h at which time there was no further evolution of hydrogen gas. A solution of epibromohydrin (**205**) (1.53 mL, 17.9 mmol) was added to the reaction mixture over a period of 30 min, and the reaction was allowed to proceed at room temperature with stirring at which time tlc indicated the reaction was complete. The solvent was removed *in vacuo*, cold water (10 mL) was added to the residue, and the mixture was extracted with ether (2 x 200 mL). The ether extract was washed with cold water, dried (Na_2SO_4), the solvent was evaporated, and the residue was dissolved in ether:hexane (6:4 v/v). The product crystallized upon cooling to yield (R,S)-(**208**) (2.21 g, 80%) as a yellow solid. The crude product (R,S)-(**208**) could also be purified by elution from a 3.0 x 60 cm silica gel column using ether:hexane (6:4 v/v) as the eluant. Removal the solvent from the 300-800 mL fraction afforded (R,S)-(**208**). The physical, ir and ^1H nmr spectral data for (R,S)-(**208**) are listed in Tables 9 and 10. (2R)-, and (2S)-1-(quinol-5-yloxy)-2,3-epoxypropanes (**209-210**) were prepared using the same procedure described for (2R,2S)-(**208**) above. Reaction of 5-hydroxyquinoline (**204**) (0.64g, 4.38 mmol) with (-)-(R)-glycidyltosylate (**206**) (1 g, 4.38 mmol) in DMF (15 mL) and NaH (0.16 g, 5.25 mmol of an 80% suspension in mineral oil) that had been washed with dry hexane under a nitrogen atmostphere was allowed to proceed at room temperature for 12 h. The solvent was removed under reduced pressure, cold water (10 mL) was added to the residue, and the mixture was extracted with ether (3 x 200 mL). The ether extract was washed with cold water, dried (Na_2SO_4), and the solvent was evaporated. The crude product was purified on a silica gel column (3,0 x 60 cm) using ether:hexane (4:6 v/v) as eluant. The first 400 mL fraction was discarded. Further elution with ether:hexane (1:1 v/v) (800 mL) afforded (-)-(R)-1-(quinol-5-yloxy)-2,3-epoxypropane (**209**) as a white cotton-like solid (0.7 g, 80%) with a R_f of 0.67 using ether as development solvent. The optical rotation for (2R)-(**209**) was $[\alpha]_D^{23}$= -27.27 (c 0.013, $CHCl_3$). The synthesis of (S)-(**210**) was performed using the same procedure as for (R)-(**209**). Reaction of 5-hydroxyquinoline (**204**) (0.57 g, 3.94 mmol) with (+)-(S)-glycidyltosylate (**207**) (0.9 g, 3.94 mmol) in DMF (15 mL) in the presence of NaH (0.14 g, 4.73 mmol, 80% suspension in mineral oil) that had been washed with dry hexane under a nitrogen atmostphere, was allowed to react at room temperature for 12 h. The crude pruduct was purified by elution from a 3.0 x 60 cm silica gel column using ether:hexane (1:1 v/v) as eluent. Removal of the solvent from the 500-1000 mL fraction gave (S)-1-(quinol-5-yloxy)-2,3-epoxypropane (**210**) as a white cotton-like solid (0.65 g, 83%) having R_f 0.67 using ether as development solvent. The optical rotation for (2S)-(**210**) was $[\alpha]_D^{23}$= +27.27 (c 0.013, $CHCl_3$). The physical, ir and ^1H nmr spectral data for (2R)-(**209**) and (2S)-(**210**) are listed in Tables 9 and 10. The enantiomeric purity of these compounds was determined by ^{1}H nmr using the chiral nmr shift reagent, Eu(hfbc)3 {tris[3-heptafluorobutyryl-d-camphorato]europium}. These results are listed in Table 11.

7.1.0.0.0 GENERAL PROCEDURE FOR THE SYNTHESIS OF (2R,2S), (2R), OR (2S)-1-(QUINOL-5-YLOXY)-3-ALKYLAMINO-2-PROPANOLS.

7.1.1.0.0 SYNTHESIS OF (2R,2S)-1-(QUINOL-5-YLOXY)-3-ISOPROPYL (OR t-BUTYL)AMINO-2-PROPANOLS (211-213).

A mixture of (2R,2S)-1-(quinol-5-yloxy)-2,3-epoxypropane (**208**) (0.3 g, 1.49 mmol) and isopropylamine (3.17 mL, 29.8 mmol), t-butylamine (2.53 mL, 29.8 mmol), or cyclohexylamine (3.31 mL, 29.8 mmol) in 2-propanol (20 mL) was stirred at 25 ºC for 24-36 h, at which time tlc indicated that (**208**) was absent. The excess amine and solvent were removed under reduced pressure, water was added to the residue (10 mL), the mixture was extracted with ethyl acetate (4 x 50 mL), dried (Na_2SO_4), and the solvent was evaporated. The residue from the selected reaction was crystallized from cold ether:hexane to give (**211**) as a white solid (0.35 g, 90%) or (**212**) as a light yellow solid (0.39 g, 96%). The residue containing (**213**) was purified by elution from a 30 x 60 cm silica gel column using chloroform as eluant. The first 400 mL fraction was discarded. Further elution with chloroform (400 ml) afforded (**213**) (0.42 g, 96%). The physical, ir and ^{1}H nmr spectral data for (2R,2S)-(**211-213**) are listed in Tables 12 and 13.

7.1.2.0.0 SYNTHESIS OF (R)-1-(QUINOL-5-YLOXY)-3-ISOPROPYL (t-BUTYL)AMINO-2-PROPANOLS (214, 215).

A mixture of (-)-(2R)-1-(quinol-5-yloxy)-2,3-epxypropane (**209**) (0.06 g, 0.2 mmol) and isopropylamine (0.5 mL, 5.96 mmol) or t-butylamine (0.73 mL, 6.95 mmol) in 2-propanol (10 mL) was stirred at 25 ^{o}C until all the epoxide had been consumed (24-36 h). The excess amine and solvent were removed under reduced pressure. The resulting liquid residue was dissolved in dry ether (40 mL) into which anhydrous HCl gas was bubbled slowly until no further formation of precipitate was observed. Removal of the solvent *in vacuo*, and crystallization of the respective product from absolute ethyl alcohol gave (**214**.2HCl) (0.09 g, 96%) and (**215**.2HCl) (0.09 g, 95%). The physical, ir and ^{1}H nmr spectral data for (2R)-(**214-215**) are presented in Tables 14 and 15.

7.1.3.0.0 SYNTHESIS OF (2S)-1-(QUINOL-5-YLOXY)-3-ISOPROPYL(t-BUTYL, OR CYCLOHEXYL)AMINO-2-PROPANOLS (216-218).

A mixture of (+)-(2S)-1-(quinolyl-5-yloxy)-2,3-epoxypropane (**210**) (0.094 g, 0.46 mmol) and isopropylamine (0.79 mL, 9.3 mmol), or (**210**) (0.068 g, 0.33 mmol) and t-butylamine (0.70 mL, 6.87 mmol) or (**210**) (0.3 g, 1.49 mmol) and cyclohexylamine (0.17 mL, 1.49 mmol) in 2-propanol (15 mL) was stirred at room temperature until all the epoxide had been consumed (24-36 h). Isolation, using the procedure described previously for (**214-215**), gave the (2S)-1-(quinol-5-yloxy)-3-isopropyl (**216**) [(or-t-butyl (**217**)]amino-2-propanol dihydrochloride salts (0.11 g and 0.09 g, respectively, 98%) as indicated in Table 16a. The crude product, (2S)-1-(quinol-5-yloxy)-3-cyclohexylamino-2-propanol (**218**) was purified by elution from a 2.0 x 40 cm silica gel column using chloroform:ethanol (3:1 v/v) as eluate. The initial 100 mL fraction was discarded. Further elution with the same solvent (300 mL) gave a residue which crystallized from cold ether upon addition of hexane to give (**218**) (0.41 g, 92%). The physical, ir and ^1H nmr spectral data for (2S)-(**216-217**. 2HCl) and (2S)-(**218**) are listed in Tables 16a and 17. The optical rotation for (**216**.2HCl) was $[\alpha]_D^{23}$= -10.84 (c 0.03, MeOH).

7.1.4.0.0 SYNTHESIS OF (2S)-1-(QUINOL-5-YLOXY)-3-(3-PHENYL PROPYLAMINO)-2-PROPANOL (219).

A mixture of (+)-(2S)-1-(quinol-5-yloxy)-2,3-epoxypropane (**210**) (0.3 g, 1.49 mmol) and 3-phenylpropylamine (0.25 mL, 1.49 mmol) in 2-propanol (15 mL) was refluxed for 5 h. The solvent was removed *in vacuo* and the residue was purified on preparative silica gel G tlc plates using ether:methanol (7:3 v/v) as the development solvent. Extraction of the band exhibiting a R_f of 0.48 with ether:methanol (7:3 v/v), using methanol gave (**219**) as an oil (0.45 g, 90%). Compound **(219)** could also be purified by silica gel column chromatography (2.0 x 40 cm) using ether:methanol (7:3 v/v) as eluant. The initial 200 mL was discarded. The desired product **(219)** was eluted in the 200-500 mL fraction. The physical, ir and ^1H nmr spectral data for (2S)-(**219**) are listed in Tables 16b and 17.

7.1.5.0.0 SYNTHESIS OF (S)-1-(QUINOL-5-YLOXY)-3-[2-(3-INDOL-YL)-1,1-DIMETHYLETHYL]AMINO-2-PROPANOL (220).

A mixture of 2-methylgramine (**223**) (1.3 g, 6.9 mmol), 2-nitropropane (4.3 mL, 49 mmol), and NaOH pellets (0.29 g, 7.2 mmol) in DMF (30 mL) was heated at reflux for (10 h). The mixture was cooled to

25 °C and filtered. This solid was dissolved in 10% AcOH (50 mL) whereupon the color changed from light brown to green. The mixture was stirred for a further 2 h at 25 °C, extracted with ether (3 x 200 mL), washed with cold water (3 x 100 mL) and dried (M[illegible]). The solvent was evaporated *in vacuo* to give (**225**) as a brown li[illegible]hich was purified by distillation (160 °C / 0.02 mm Hg) to affor[illegible] liquid which slowly crystallized on standing at 25 °C to a solid (1.35 g, 90%), mp 73-74 °C (lit.[446] mp= 72-74 °C). Alternatively, the product could be purified by silica gel column chromatography (2 x 40 cm) using ether:hexane (6:4 v/v) as eluant where the desired product was present in the 300-700 mL fraction. Ir (KBr): indole NH (3414) and NO_2 (1534, 1342) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.65 (s, 6 H, $-CH_2C(\underline{CH_3})_2NO_2$); 3.38 (s, 2H, $-\underline{CH_2}C(CH_3)_2NO_2$); 7.0 (d, J_{CH-NH}= 2Hz, 1H, indolyl H-2); 7.14 (d, $J_{5,6}$= 8.0 Hz of d, $J_{6,7}$= 8.0 Hz, of d, $J_{4,6}$= 1.5 Hz, 1H, indolyl H-6); 7.2 (d, $J_{4,5}$= 8.0 Hz of d, $J_{5,6}$= 8.0 Hz of d, $J_{5,7}$= 1.5 Hz, 1H, indolyl H-5); 7.38 (d, $J_{4,5}$= 8.0 Hz of d, $J_{4,6}$= 1.5 Hz, 1H, indolyl H-4); 7.56 (d, $J_{6,7}$= 8.0 Hz of d, $J_{5,7}$= 1.5 Hz, 1H, indolyl H-7); 8.1 (br s, 1H, indolyl -NH, exchanges with deuterium oxide).

3-(2,2-Dimethyl-2-nitroethyl)-1H-indole (**225**) (1.35 g, 6.2 mmol) was added to 95% ethanol (150 mL), palladium-on-charcoal (0.5 g, 10%) and hydrazine hydrate (0.8 mL, 25.2 mmol). The resulting dark red mixture was refluxed for 2 h to give a colorless solution which was filtered, while still hot, through Celite. The filter cake was washed with hot ethanol (25 mL), the combined filtrates were dried (Na_2SO_4), and the solvent was removed *in vacuo*. Crystallization of the residue from ether:chloroform afforded 3-(2,2-dimethyl-2-aminoethyl)-1H-indole (**226**) as a white solid (0.9 g, 80%), mp 129-130 °C; ir (KBr): indole NH

(3412) and NH_2 (3280 and 3349) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 1.20 (s, 6H, -$CH_2C(\underline{CH}_3)_2NH_2$); 1.36 [br s, 2H, -$CH_2C(CH_3)_2\underline{NH}_2$, exchange with deuterium oxide]; 2.84 (s, 2H, -$\underline{CH}_2C(CH_3)_2$); 7.04 (s, 1H, indolyl H-2); 7.13 (d, $J_{5,6}$= 8.0 Hz of d, $J_{6,7}$= 8.0 Hz, 1H, indolyl H-6); 7.19 (d, $J_{4,5}$= 8.0 Hz of d, $J_{5,6}$= 8.0 Hz, 1H, indolyl H-5); 7.36 (d, $J_{4,5}$= 8.0 Hz, 1H, indolyl H-4); 7.64 (d, $J_{6,7}$= 8.0 Hz, 1H, indolyl H-7); 8.52 (br s, 1H, indolyl -NH, exchanges with deuterium oxide).

A mixture of (+)-(S)-1-(quinol-5-yloxy)-2,3-epoxypropane (**210**) (0.5 g, 2.48 mmol) and 3-(2,2-dimethyl-2-aminoethyl)-1H-indole (**226**) (0.46 g, 2.48 mmol) in 2-propanol (12 mL) was refluxed for 12 h. Removal of the solvent *in vacuo* gave a residue which was purified by recrystallization from ether:hexane or on silica gel G plates with ether:ethanol (3:1 v/v) as development solvent. Extraction of the band having R_f 0.48 with chloroform:ethanol (7:3 v/v) as development solvent, with methanol gave (S)-1-(quinol-5-yloxy)-3-[2-(3-indolyl)-1,1-dimethylethyl]amino-2-propanol (**220**) (0.77 g, 80%), mp 80 °C. The structure assigned to (**220**) was consistent with its ir and ^1H nmr spectral data. The ir and ^1H nmr spectral data for (**220**) are listed in Tables 16b and 17.

7.1.6.0.0 SYNTHESIS OF (2S)-1-(QUINOL-5-YLOXY)-3-[(S)-α-METHYLBENZYL]AMINO-2-PROPANOL (221).

A mixture of (+)-(S)-1-(quinol-5-yloxy)-2,3-epoxypropane (**210**) (0.2 g, 0.99 mmol) and (-)-(S)-α-methylbenzylamine (0.12 g, 0.99 mmol) in 2-propanol (10 mL) was stirred at 25 °C for 36 h. The solvent was evaporated *in vacuo* to give a crude residue which was purified either by recrystallization from ether:hexane upon cooling, or by silica gel column chromatography (2 x 40 cm) starting with chloroform (300 mL) and increasing the amount of ethanol to obtain a final solvent mixture containing chloroform:ethanol (8:2 v/v) as eluant. The target product (**221**) was present in the 300-600 ml fraction and was obtained as a white solid (0.3 g, 95%), mp 59 °C, R_f 0.55 using ether:ethanol (7:3 v/v) as tlc development solvent. The physical, ir and ^{1}H nmr spectral data are shown in Tables 16b and 17.

7.1.7.0.0 SYNTHESIS OF (2S)-1-(QUINOL-5-YLOXY)-3-[1-(4-DIPHENYLMETHYL)PIPERAZINYL]AMINO-2-PROPANOL (222).

NaH (0.46 g, 13.93 mmol, 60% suspension in mineral oil) was washed with dry hexane and dried under a nitrogen atmosphere and suspended in DMF (5 mL). A solution of piperazine (1 g, 11.6 mmol) in DMF (15 mL) was added dropwise under a nitrogen atmosphere at 0 °C and the mixture was stirred for 3 hr at 25 °C. A solution of bromodiphenylmethane (2.86 g, 11.6 mmol) in DMF (40 mL) was then added during a period of 1.5 h. After stirring for 18 h at 25 °C, the mixture was filtered, the filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (3 x 60 cm) using chloroform as eluant. The desired product was obtained in the colorless 300-700 mL fraction. Removal of the solvent gave (**229**) as a white solid (2.64 g, 90%), mp 78 °C. Ir (KBr): NH (3400) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.52 (s, 1H, NH, exchanges with deuterium oxide); 2.36 (br m, 4H, $H\text{-}N(\underline{CH}_2)_2(CH_2)_2N\text{-}CH(Ph)_2$]; 2.88 (t, J= 4.97 Hz, 4H, $H\text{-}N(CH_2)_2(\underline{CH}_2)_2N\text{-}CH(Ph)_2$]; 4.21 [s, 1H, $HN(CH_2)_2(CH_2)_2N\text{-}\underline{CH}(Ph)_2$]; 7.18 (t, 2H, J= 7.5 Hz, phenyl *para*-hydrogens); 7.27 (t, 4H, J= 7.5 Hz, phenyl *meta*-hydrogens); 7.42 (d, J= 7.5 Hz, 4H, phenyl *ortho*-hydrogens). Microanalysis for $C_{17}H_{20}N_2$: found (calcd.) C, 81.22 (80.91); H, 7.98 (7.98); N, 11.14 (11.10).

The reaction of (+)-(2S)-1-(quinol-5-yloxy)-2,3-epoxypropane (**210**) (0.3 g, 1.49 mmol) with (**229**) (0.37 g, 1.49 mmol) in 2-propanol (10 mL) was allowed to proceed for 5 h at reflux followed by stirring at 25 °C for a further 12 h. The solvent was evaporated *in vacuo* to afford a liquid which was recrystallized from ether:hexane to give (**222**) (0.62 g, 93%), mp 139 °C. The physical, ir and ^{1}H nmr spectral data for (**222**) are listed in Tables 16b and 17.

7.2.0.0.0 GENERAL PROCEDURE FOR THE SYNTHESIS OF (2R,2S), -1-(QUINOL-4-YLOXY)-2,3-EPOXYPROPANE (231a) AND 1-[1-(1,4-DIHYDROQUINOLIN-4-ONE)]-2,3-EPOXYPROPANE (232a), METHOD A IN SCHEME 24.

NaH (0.5 g, 16.53 mmol, 80% suspension in mineral oil) was washed with dry hexane, dried under a nitrogen atmosphere, and suspended in DMF (10 mL). A solution of 4-hydroxyquinoline (**230**) (2 g, 13.7 mmol) in DMF (30 mL) was added dropwise at 0 °C. The reaction mixture was heated at 50 °C for 30 min, allowed to cool to 25 °C and stirred until there was no further evolution of hydrogen gas (3 h). A solution of epibromohydrin (**205**) (1.41 mL, 16.53 mmol) in DMF (10 mL) was added during a period of 30 min, the reaction was allowed to continue with stirring for 18 h at 25 °C, and the excess DMF was partially removed under reduced pressure. The mixture was poured into ice-water (10 mL), extracted with chloroform (200 x 3 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a mixture of O-alkylated (**231a**) and N-alkylated (**232a**) products which were separated by fractional crystallization. The solid obtained was filtered and recrystallized from ether:hexane to yield pure 1-(1-quinolin-4-one)-2,3-epoxypropane **(232a)** (1.9 g, 68%) as a light yellow solid, mp 106 °C. The filtrate containing a mixture of predominantly **(231a)**, together with some additional **(232a)** was then concentrated and separated on silica gel G tlc plates using ether: ethanol (9:1 v/v) as development solvent. Extraction of the band having R_f 0.48 with methanol gave (2R,2S)-1-(quinol-4-yloxy)-2,3-epoxypropane **(231a)** (0.27 g, 10%) as an oil, and the band having R_f 0.1 with methanol gave **(232a)** (0.07 g, 3%). The structure assigned to **(231a)** and **(232a)** were consistent with their ir and ^1H nmr spectral data which are listed in Table 18.

7.2.1.0.0 SYNTHESIS OF (2R,2S)-1-(QUINOL-4-YLOXY)-3-ISOPROPYL AMINO-2-PROPANOL (233a) AND 1-[1-(1,4-DIHYDROQUINOLIN-4-ONE)]-3-ISOPROPYLAMINO-2-PROPANOL (234a).

METHOD A IN SCHEME 24.

A mixture of (R,S)-1-(quinol-4-yloxy)-2,3-epoxypropane **(231a)** (0.2 g, 0.99 mmol) or (R,S)-1-[1-(1,4-dihydroquinolin-4-one)-2,3-epoxypropane **(232a)** (0.2 g, 0.99 mmol) in 2-propanol (10 mL) was stirred at 25 °C for 36 h. The solvent was evaporated *in vacuo* to give a crude residue which was purified by recrystallization from ether: hexane to provide (R,S)-**(233a)** (0.23 g, 92%), mp 61-62 °C, and from chloroform: hexane to afford (R,S)-**(234a)** (0.24 g, 95%), mp 127 °C. The physical, ir and ^1H nmr spectral data for (R,S)-**(233a)** and (R,S)-**(234a)** are listed in Tables 20 and 21. Compound **(234a)** was dissolved in dry ether (50 mL) into which anhydrous HCl gas was bubbled slowly until no further formation of precipitate was observed. Removal of the solvent *in vacuo* and recrystallization of the respective product from

absolute alcohol gave (**234a**. 2HCl). Ir (KBr): OH (3353), C=O (1626), C=C (1607), C–O (1239) cm^{-1}; 1H nmr (CDCl$_3$ and DMSO-d$_6$): 1.33 [m, 6H, $-CH(\underline{CH}_3)_2$]; 3.05 [br m, 1H, $-C\underline{H}H^1-NH(HCl)-$]; 3.35 (br m, 2H, $-CH\underline{H}^1-NH(HCl)-$, $-NH-\underline{CH}(CH_3)_2$]; 4.34 [br m, 2H, quinolone-$C\underline{H}H^1-CH(OH)-$, quinolone-$CHH^1-\underline{CH}(OH)-$], 4.40 (br s, 2H, $O\underline{H}$ and $N\underline{H}$, exchange with deuterium oxide); 4.86 [br m, 1H, quinolone-$CH\underline{H}^1-CH(OH)-$]; 6.70 [d, $J_{2,3}$= 8.1 Hz, 1H, quinolone H-3]; 7.65 [d, $J_{5,6}$= 7.42 Hz of d, $J_{6,7}$= 7.42 Hz, 1H, quinolone H-6]; 7.96 [d, $J_{6,7}$= 7.42 Hz of d, $J_{7,8}$= 7.42 Hz of d, $J_{5,7}$= 1.35 Hz, 1H, quinolone H-7]; 8.19 (d, $J_{7,8}$= 7.42 Hz, 1H, quinolone H-8]; 8.38 (d, $J_{5,6}$= 7.42 Hz of d, $J_{5,7}$= 1.35 Hz, 1H, quinolone H-5]; 8.40 (d, $J_{2,3}$= 8.1 Hz, 1H, quinolone H-2]; 7.77 and 9.0 (two br s, 1H each, NH, exchanges with deuterium oxide). Microanalysis for $C_{15}H_{20}N_2O_2$, 2HCl: found (calcd.) C, 53.57 (54.05); H, 6.46 (6.65); N, 8.10 (8.40).

7.2.2.0.0 SYNTHESIS OF (2S)-1-(QUINOL-4-YLOXY)-3-ISOPROPYLAMINO-2-PROPANOL(233a') AND (2S)-1-[1-(1,4-DIHYDROQUINOLIN-4-ONE)]-3-ISOPROPYLAMINO-2-PROPANOL (234a') METHOD A IN SCHEME 24.

(2S)-1-(quinol-4-yloxy)-2,3-epoxypropane (**231a'**) and (2S)-1-[1-(1,4-dihydroquinolin-4-one)]-2,3-epoxypropane (**232a'**) were prepared using the same procedure described for the synthesis of (**231a** or **232a**) in section 8.4.0.0.0. Reaction of 4-hydroxyquinoline (**230**) (0.64 g, 4.38 mmol) with (+)-(2S)-glycidyltosylate (**207**) (1 g, 4.38 mmol) in DMF (15 mL) and NaH (0.16 g, 5.25 mmol of an 80% suspension in mineral oil that had been washed with dry hexane under a nitrogen atmosphere), was allowed to proceed at 25 ^{o}C for 10 h with stirring. The solvent was removed under reduced pressure, cold water (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate (2 x 200 mL). The extract was washed with cold water (2 x 50 mL), dried (Na_2SO_4), and the solvent was removed *in vacuo*. The crude product was purified on silica gel G tlc plates using ether:ethanol (9:1 v/v) as development solvent. Extraction of the band having R_f 0.4 with methanol gave (S)-(**231a'**) (0.08 g, 10%) as an oil. Extraction of the band having R_f 0.1 with methanol gave (S)-(**232a'**) (0.57 g, 65%) as an oil which was used without characterization. The ir and ^{1}H nmr spectral data for (S)-(**231a'**) are listed in Table 18. Subsequently, a mixture of (S)-(**231a'**) (0.08 g, 0.39 mmol) and isopropylamine (0.5 mL, 5.96 mmol), or (S)-(**232a'**)(0.3 g, 1.49 mmol) and isopropylamine (3.5 mL, 32.9 mmol), in 2-propanol (10 mL) was allowed to react at 25 °C for 24 h, at which time tlc indicated that (S)-(**231a'**) or (S)-(**232a'**) was absent. Removal of the excess amine and solvent gave (S)-(**233a'**) (0.09 g, 97%) as an oil which was converted to the dihydrochroride salt, using the procedure described for (**234a**), to afford (S)-(**233a'**, 2HCl), mp 207 °C; or (s)-(**234a'**) which was purified by crystallization from chloroform:hexane to give (0.34 g, 90%) as a white solid, mp 127 °C. The physical data for (S)-(**233a'**, 2HCl) is listed in Table 20. The ir and ^{1}H nmr spectral data for (S)-(**233a'**, 2HCl) and (s)-(**234a'**) are presented in Table 21.

7.2.3.0.0 PREPARATION OF 2-PHENYL-3-ISOPROPYL(OR t-BUTYL)-5-(HYDROXYMETHYL)OXAZOLIDINES (193 a,b).

Isopropylamine (15 mL, 0.17 mol) or t-butylamine (15 mL, 0.12 mol) was added dropwise to glycidol (**235**) (5 mL, 74.66 mmol) at 0°C and the reaction mixture was stirred at 25 °C for 24 h. The excess alkylamine was removed *in vacuo* to give the respective 3-isopropylamino-1,2-propanediol (**236a**) which was distilled (80-85 °C / 0.1 mm Hg) (9.7 g, 97%) as an oil, or 3-t-butylamino-1,2-propanediol (**236b**) which was washed with ether:hexane (1:1 v/v), filtered and dried to yield a white solid (10.8 g, 98%); mp 68-69 °C; Ir (KBr): OH (3254) (cm^{-1}). Subsequently , a mixture of (**236a**) or (**236b**) and benzaldehyde (20 mL) was heated at 160-180 °C in an oil bath for 5-6 h. The mixture was cooled to 25 °C and distilled under reduced pressure to give 2-phenyl-3-isopropyl-5-hydroxymethyloxazolidine^{450} (**193a**) which was distilled at 145-150 °C / 0.2 mm Hg to yield an oil (12.9 g, 80%), or a mixture of 2-phenyl-3-t-butyl-5-hydroxymethyloxazolidine (**193b**) and 2-phenyl-5-t-butylaminomethyl-1,3-dioxolidine (**237b**) which was distilled (120-125 °C / 0.2 mm Hg) to give an oil (15.5 g, 90%). The mixture of (**193b**) and (**237b**) which was separated by elution from a 7.5 x 80 cm^{-1} silica gel column chromatography using ether:hexane (8:2 v/v) as eluant gave (**193b**) (12.4 g, 80%) and (**237b**) as an oil. Two diastereomers [RR(SS), RS(SR)] of (**237b**) were separated on silica gel G tlc plates using ether as development solvent. Extraction of the band having R_f= 0.55 and 0.3 with methanol yielded two pure diastereomers (**237b', 237b''**) as oils (1.2 g each). The ir and ^{1}H nmr spectral data for (**236 a,b**), (**193 a,b**), and (**237 b', b''**) are listed in Table 19. Microanalysis for (**193b**) $C_{14}H_{21}NO_2$; found (calcd.) C, 71.0 (71.45); H, 9.03 (8.99); N, 5.94 (5.95).

7.2.3.1.0 SYNTHESIS OF (R,S)-1-(QUINOL-4-YLOXY)-3-ISOPROPYL AMINO-2-PROPANOL (233a).

METHOD B IN SCHEME 25.

The synthesis of (**233a**) which was outlined in Scheme 24 method A were prepared by an alternative procedure as described in Scheme 25, method B. NaH (0.22 g, 7.33 mmol, 80% suspension in mineral oil) was washed with dry hexane and dried under a nitrogen atmosphere prior to addition of DMF (10 mL). A solution of 2-phenyl-3-isopropyl-5-hydroxymethyloxazolidine (**193a**) (1.35 g, 6 mmol) in DMF (30 mL) was added dropwise under a nitrogen atmosphere at 0 °C, the reaction mixture was heated in an oil bath at 70 °C for 30 min, and then at 25 °C for 4 h with stirring. A solution of 4-chloroquinoline (**238**) (1 g, 6 mmol) in DMF (30 mL) was then added dropwise over a period of 30 min, and the mixture was stirred for 24 h at 25 °C. Excess DMF was partially removed under reduced pressure, the reaction mixture was poured into ice-water and extracted with ether (3 x 200 mL). The combined extracts were washed with cold water, dried (Na_2SO_4) and the solvent was removed in vacuo to give 2-phenyl-3-isopropyl-5-[(quinol-4-yloxy)methyl]oxazolidine (**239**) as an oil having R_f 0.41 with ether:methanol (8:2 v/v) as development solvent (see Scheme 25). Compound (**239**) was dissolved in 1.5 N HCl (25 mL), and the solution was heated on a steam bath for 1 h prior to stirring at 25 °C for an additional 1 h. This acidic solution was poured into a cold solution of saturated Na_2CO_3, basified to pH 9-10 and extracted with ether (3 x 200 mL). The organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was crystallized from ether:hexane to give (**233a**) (1.45 g, 92%), mp 61-62 °C. This product was identical (mp) to that prepared using the procedure described in Scheme 24, method A. The physical, ir and ^1H nmr spectral data for **(233a)** are presented in Tables 20 and 21.

7.3.0.0.0 SYNTHESIS OF (2R,2S)-1-(QUINOL-2-YLOXY)-3-ISOPROPYL (OR t-BUTYL)AMINO-2-PROPANOLS (242 a,b).

The syntheses of **(242a)** and **(242b)** were carried out using method B outlined in Scheme 25 as described for **(233a)**. Reaction of **(240)** (1 g, 6.1 mmol) and **(193a)** (1.35 g, 6 mmol) in the presence of NaH (0.22 g, 7.33 mmol, 80% suspension in mineral oil), that had been washed with dry hexane prior to addition of DMF under a nitrogen atmosphere at 25 °C for 24 h, extraction with ethyl acetate, drying (Na_2SO_4) and removal of the solvent *in vacuo* yielded the intermediate 2-phenyl-3-isopropyl-5-[(quinol-2-yloxy)methyl]oxazolidine **(241a)**. This product was recrystallized from ether to provide **(241a)** as a solid, mp 62 °C, having R_f 0.56 using ether as development solvent. Compound **(241a)** was dissolved in 1.5 N HCl (25 mL), and the solution was heated on a steam bath for 1 hr prior to stirring at 25 °C for an additional 1 h. This acidic solution was poured into a cold solution of saturated Na_2CO_3, basified to pH 9-10 and extracted with ether (3 x 200 mL). The organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo* to yield **(242a)** as a white solid (1.40 g, 90%), mp 130-131 °C. The physical, ir and ^1H nmr spectral data for **(242a)** are summarized in Tables 20 and 21. Similarly, the reaction of **(240)** (1 g, 6.1 mmol) with **(193b)** (1.41 g, 6 mmol) in the presence of NaH (0.22 g, 7.33 mmol, 80% suspension in mineral oil) gave 2-phenyl-3-t-butyl-5-[(quinol-2-yloxy)methyl]oxazolidine **(241b)** as a solid, mp 123 °C, having R_f 0.56 with ether as development solvent. Ir (KBr): C=N (1619), C=C (1603), aromatic C-O (1274), aliphatic C-O (1257), oxazolidinyl C-O (1110 and 1239) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ : 1.18 (s, 9H, t-Bu); 3.0 (d, J_{gem}= 8.73 Hz of d, J_{vic}= 8.73 Hz, 1H, oxazolidinyl $\underline{H}H^1$-4); 3.5 (d, J_{gem}= 8.73 Hz of d, J_{vic}= 8.73 Hz, 1H, oxazolidinyl $H\underline{H}^1$-4); 4.43 (m, 1H, oxazolidinyl H-5); 4.59 (d, J_{vic}= 5.82 Hz of d, J_{gem}= 12.12 Hz, 1H, -O-C$\underline{H}H^1$-oxazolidinyl); 4.69 (d, J_{vic}= 3.88 Hz of d, J_{gem}= 12.12 Hz, 1H, -O-CH$\underline{H}^1$-oxazolidinyl); 5.82 (s, 1H, oxazolidinyl H-2); 6.91 (d, $J_{3,4}$= 8.6 Hz 1H, quinolyl H-3); 7.32 (m, 5H, phenyl hydrogens) ; 7.40 (d, $J_{5,6}$= 7.9 Hz of d, $J_{6,7}$= 7.9 Hz of d, $J_{6,8}$= 1.3 Hz, 1H, quinolyl H-6); 7.66 (d, $J_{6,7}$= 7.9 Hz of d, $J_{7,8}$= 7.9 Hz of d, $J_{5,7}$= 1.3 Hz, 1H, quinolyl H-7); 7.74 (d, $J_{5,6}$= 7.9 Hz of d, $J_{5,7}$= 1.3 Hz, 1H, quinolyl H-5); 7.84 (d, $J_{7,8}$= 7.9 Hz, 1H, quinolyl H-8); 8.0 (d, $J_{3,4}$= 8.6 Hz, 1H, quinolyl H-4). Microanalysis for $C_{23}H_{26}N_2O_2$; found (calcd.) C, 76.11 (76.21); H, 7.20 (7.23); N, 7.56 (7.73).

Compound (**241a**) was dissolved in 1.5 N HCl (25 mL), and the solution was heated on a steam bath for 1 h prior to stirring at 25 ^oC for an additional 1 h. This acidic solution was poured into a cold solution of saturated Na_2CO_3, basified to pH 10 and extracted with ether (3 x 200 mL). The organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo* to yield (**242b**) as a solid (1.49 g, 91%), mp 130-131 ^oC. The physical, ir and ^{1}H nmr spectral data for (**242b**) are summarized in Tables 20 and 21.

7.4.0.0.0 SYNTHESIS OF (2R,2S)-1-(PYRIMIDIN-2-YLOXY)-3-ISOPROPYL (OR t-BUTYL)AMINO-2-PROPANOLS (245 a,b).

Compounds (**245 a,b**) outlined in Scheme 26 were prepared using the procedure described for the synthesis of (**233a**). Reaction of

2-chloropyrimidine (1 g, 8.7 mmol) with (**193a**) (1.93 g, 8.7 mmol) or (**193b**) (2.05 g, 8.7 mmol) in the presence of NaH (0.41 g, 10.5 mmol, 60% suspension in mineral oil) gave 2-phenyl-3-isopropyl (or t-butyl)-5-[(pyrimidin-2-yloxy)methyl]oxazolidine (**244a**) or (**244b**) as an oil having R_f 0.52 and 0.62, respectively with ether:hexane (8:2 v/v) as development solvent. The ^{1}H nmr spectral data for (**244a**) and (**244b**) are listed in Table 23. Compound (**244a**) or (**244b**) was dissolved in 1.5 N HCl (20 mL), and the solution was heated on a steam bath for 45 min prior to stirring at 25 °C for an additional 1 h. This acidic solution was poured into a cold solution of saturated Na_2CO_3, basified to pH 10 and extracted with ether (3 x 200 mL). The organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo* to yield (**245a**) (1.65 g, 90%) as a solid, mp 52 °C; and (**245b**) (1.80 g, 92%), mp 82 °C. The physical, ir and ^{1}H nmr spectral data for (**245a** and **245b**) are summarized in Tables 22 and 23.

7.5.0.0.0 GENERAL SYNTHESIS OF (2R,2S),-1-(ISOQUINOL-5-YLOXY)-3-ALKYL(ALKYLARYL)AMINO-2-PROPANOLS (248-251).

The syntheses of (**248-251**) are outlined in Scheme 27.

7.5.1.0.0 SYNTHESIS OF (2R,2S)-1-(ISOQUINOL-5-YLOXY)-2,3-EPOXYPROPANE (247).

Sodium hydride (0.96 g, 24 mmol, 60% emulsion in mineral oil) was washed with dry hexane and dried under a nitrogen atmosphere prior to addition of DMF (10 mL). A solution of 5-hydroxyisoquinoline (**246**) (3 g, 20 mmol) in DMF (60 mL) was added dropwise under a nitrogen atmosphere at 0 °C, the mixture was stirred at 50 °C for 30 min and then at 25 °C until no further evolution of hydrogen gas was observed (4 h). A solution of epibromohydrin (**205**) (2.12 mL, 24 mmol) in DMF (15 mL) was added during 30 min, the mixture was stirred for 18 h at 25 °C and the excess DMF was partially removed under reduced pressure. The mixture was poured into ice-water (20 mL), extracted with ether (3 x 300 mL), dried (Na_2SO_4) and the solvent was removed *in vacuo* to give 1-(isoquinol-5-yloxy)-2,3-epoxypropane (**247**). This product was purified by elution from a 3 x 60 cm silica gel column using ether:hexane (8:2 v/v) as eluant Removal of the solvent from the 300-1000 mL fraction afforded pure (**247**) as an oil (3.45 g, 85%). The physical, ir and ^1H nmr spectral data for (**247**) are summarized in Tables 24 and 25.

7.5.2.0.0 SYNTHESIS OF (2R,2S)-1-(ISOQUINOL-5-YLOXY)-3-ISOPROPYL(OR t-BUTYL)AMINO-2-PROPANOLS (248-249).

A mixture of 1-(isoquinol-5-yloxy)-2,3-epoxypropane (**247**) (0.1 g, 0.5 mmol) and isopropylamine (0.5 mL, 5.96 mmol) or t-butylamine (0.73 mL, 6.95 mmol) in 2-propanol (10 mL) was allowed to stir at 25 °C until all the epoxide had reacted (24-36 h). Excess amine and solvent were removed *in vacuo* to give (**248-249**), respectively as solids in 98% yield. Compounds (**248-249**) could be recrystallized from ether. The physical, ir and ^1H nmr spectral data for (**248-249**) are summarized in Tables 24 and 25.

7.5.3.0.0 SYNTHESIS OF (2R,2S)-1-(ISOQUINOL-5-YLOXY)-3-CYCLOHEXYLAMINO-2-PROPANOL (250) AND (2R,2S)-1-(ISOQUINOL-5-YLOXY)-3-PHENYLPROPYLAMINO-2-PROPANOL (251).

A mixture of 1-(isoquinol-5-yloxy)-2,3-epoxypropane (**247**) (0.5 g, 2.5 mmol) and cyclohexylamine (0.28 mL, 2.5 mmol) or 3-phenyl-1-propylamine (0.35 mL, 2.5 mmol) in 2-propanol (10 mL) was heated at reflux for 3 h prior to stirring at 25 °C for an additional 2 h. Removal of the solvent *in vacuo* and recrystallization from cold ether gave (**250**) and (**251**) as solids in 92 and 90% yield, respectively. The physical, ir and ^{1}H nmr data for (**250**) and (**251**) were summarized in Tables 24 and 25.

7.6.0.0.0 SYNTHESIS OF (2R,2S)-1-[2-(ISOQUINOLIN-1-ONE)]-2,3-EPOXYPROPANE (253).

Sodium hydride (0.96 g, 24 mmol, 60% suspension in mineral oil) was washed with dry hexane and dried under a nitrogen atmosphere prior to addition of DMF (10 mL). A solution of 1-hydroxyisoquinoline (**252**) (3 g, 20 mmol) in DMF (60 mL) was added dropwise under a nitrogen atmosphere at 0° C, the mixture was stirred at 50 °C for 30 min and then at 25 °C until no further evolution of hydrogen gas was evident (2 h). A solution of epibromohydrin (**205**) (2.12 mL, 24 mmol) in DMF (15 mL) was added during 15 min at which time the color changed from a brown to green color. After stirring for 18 h at 25 °C, the excess DMF was partially removed under reduced pressure. The mixture was poured into ice-water (20 mL), extracted with ether (3 x 300 mL), dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield 1-[2-(isoquinolin-1-one)-2,3-epoxypropane (**253**). This product was purified by elution from a 3 x 60 cm silica gel column using ether as eluant. Removal of the solvent from the 400-1000 mL fraction afforded pure (**253**) as a white solid (3.45 g, 85%). The physical, ir and ^{1}H nmr spectral data for (**253**) are summarized in Tables 26 and 27.

7.6.1.0.0 SYNTHESIS OF (2R,2S)-1-[2-(ISOQUINOLIN-1-ONE)]-3-ISOPROPYL(t-BUTYL OR CYCLOHEXYL)AMINO-2-PROPANOLS (254-256).

A mixture of 1-[2-(isoquinolin-1-one)-2,3-epoxypropane (**253**) (0.5 g, 2.5 mmol) and isopropylamine (0.5 mL, 5.96 mmol) or t-butylamine (0.73 mL, 6.95 mmol) or cyclohexylamine (0.28 mL, 2.5 mmol) in 2-propanol (10 mL) was stirred at 25 ^{o}C until the reaction was complete as indicated by tlc (20-36 h). The solvent was removed *in vacuo* to afford the respective products (**254-256**) as solids in 92-98% yield. The physical, ir and ^{1}H nmr spectral data for (**254-256**) are summarized in Tables 26 and 27.

7.7.0.0.0 SYNTHESIS OF (2R,2S)-1-[3-(QUINAZOLIN-4-ONE)]-3-ISOPROPYL(t-BUTYL)AMINO-2-PROPANOLS (259-260).

Sodium hydride (0.8 g, 26.7 mmol, 80% suspension in mineral oil) was washed with dry hexane and dried under a nitrogen atmosphere prior to addition of DMF (15 mL). A solution of 4-hydroxyquinazoline (**257**) (3 g, 20.5 mmol) in DMF (80 mL) was added dropwise under a nitrogen atmosphere at 0 ^{o}C, the mixture was stirred at 50 ^{o}C for 30 min and then at 25 ^{o}C until no further evolution of hydrogen gas was evident (2 h). A solution of epibromohydrin (**205**) (2.28 mL, 26.68 mmol) in DMF (15 mL) was added during 30 min, the reaction was stirred for 15 h at 25 ^{o}C, the excess DMF was partially removed under reduced pressure. The mixture was poured into ice-water (20 mL), extracted with ether (3 x 300 mL), dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield 1-[3-(quinazolin-4-one)-2,3-epxypropane (**258**). This product was purified by recrystallization from ether to give pure (**258**) (3.23 g, 78 %) as a white solid, mp 86 °C. The physical, ir and ^{1}H nmr spectral data for (**258**) are summarized in Tables 28 and 29. Subsequently, a mixture of (**258**) (0.5 g, 2.47 mmol) and isopropylamine (0.85 mL, 10 mmol) or t-butylamine (1.05 mL, 10 mmol) was stirred at 25 °C for 18-24 h. The solvent was evaporated *in vacuo* and the crude product was recrystallized from ether to yield the respective product (**259** or **260**) as a solid in 98% yield. The physical, ir and ^{1}H nmr spectral data for (**258-260**) are summarized in Tables 28 and 29.

7.8.0.0.0 SYNTHESIS OF 1-(3-CYANO-2-PYRIDYLOXY)-3-ISOPROPYL AMINO-2-PROPANOL (264) AND 1-(2-PYRIDYLOXY)-3-ISOPROPYLAMINO-2-PROPANOL (265).

A mixture of nicotinamide-1-oxide (**261a**) (4.25 g, 0.03 mol) and phosphorous pentachloride (12.81 g, 0.06 mol) was stirred thoroughly. Phosphorous oxychloride (12.0 mL) was added slowly with skaking. The flask was then placed in an oil bath that was preheated to 50-60 °C. The temperature was then raised up to 100 °C. The evolution of hydrogen chloride gas increased in the 90-100 °C range, and a spontaneous vigorous refluxing of the phosphorous oxychloride began. The reaction flask temperature was controlled by cooling in an ice-water bath, as required until the vigorous reaction had subsided. The oil bath was removed and the reaction mixture was heated under reflux at 115-120 °C for 1.5 h. After cooling, excess phosphorous oxychloride was removed by distillation under reduced pressure. The residue was poured into 300 mL ice-water, stirred at 5 °C overnight and extracted with ether (2 x 300 mL). The ether extracts were washed with 5 % NaOH and the ether layer was washed with water until the water extract was no longer alkaline. Charcoal (50 mg) was added to the ether solution which was heated at refluxed for 10 min, filtered, dried (Na_2SO_4) and the solvent was removed *in vacuo* to give a white solid (**261b**) (1.6 g, 38%), mp 105-106 °C (lit[466]. 105-106 °C). Subsequently, reaction of 2-chloro-3-cyanopyridine (**261**) or 2-chloropyridine (**261b**) with (**193a**) in the presence of NaH, as described previously for the synthesis of (**233a**) gave (**264**) and (**265**), respectively. The physical, ir and ^1H nmr spectral data for (**264-265**) are summarized in Tables 30 and 31.

8.0.0.0.0 PHARMACOLOGICAL TEST PROCEDURE.

8.1.0.0.0 DETERMINATION OF GUINEA PIG ATRIA CHRONOTROPIC AND INOTROPIC RESPONSES.

White male guinea-pigs (GP) between 400-600 g in weight were killed by a blow to the head, bled and then decapitated. The chest wall was opened, the heart was removed as quickly as possible and placed in a container of Hepes solution (pH 7.4). All ventricular tissue was cut away, the right and left atrium were carefully dissected, separated with great care, and freed from adhesive tissue. The right atrium is more elongated, should be spontaneously beating due to S-A mode; and the left atria is lobe-like. A polyester thread was tied to the upper most and another to the lower part of the right and left atrium tissue in proper geometry. The spontaneously beating right atrium was placed in the glass jacketed water baths (10 mL) containing Hepes solution (HPSS) at 37 ^{o}C, and held in place midway down, by tucking the bottom thread into the rubber tubing (see Fig. 16). The individual organ bath was aerated with oxygen by using syringes connected to the oxygen tank and inserted into the rubber tubing (Fig. 16). The rates of bubbling oxygen were adjusted to give a steady streams of small bubbles The temperature was maintained by a constant temperature circulator (Haake Model E52). The upper end of the muscle was connected to a Force transducer (Grass FT03) under a resting tension of approximately 0.75 g. Isometric tension was then recorded on a Grass polygraph (Model 7D). The right atrium should start to beat spontaneously once placed in the bath. The rate of beating was recorded using a Grass force-displacement transducer as described above and the rate was counted. The procedure for the left atrium differed from that of the right atrium in that the bottom thread was used to anchor the left atrium to a stimulating electrode. The back side of the left atrium should be in contact with the wires of electrode. The electrode and tissue were placed in the glass organ bath (10 mL) containing Hepes solution (HPSS) at 37 ^{o}C, adjusted to the appropriate position, using the clamp and aerated with oxygen at the proper rate as described for the right atrium. The upper end of the muscle was connected to a Force transducer (Grass FT03) under a resting tension of approximately 0.75 g and the isometric tension was then recorded on a Grass polygraph (Model 7D). The isolated left atrium was electrically stimulated at a constant rate by square pulses of 1.5 msec duration and an intensity approximately twice that of threshold (2.0 volts). The pulses were delivered by an electronic stimulator (Grass S44) through an isolation unit (Grass SIU5) at a stimulation rate of 2 to 4 Hz, which corresponded to 85-95 per cent of the maximal activity. Following a 45 min equilibration period during which the physiological medium solution was changed every 15 min, cumulative dose-response curves for the agonist isoproterenol dihydrochloride (increments of half-log units from 10^{-10} to 3×10^{-7} M) were prepared for right and left atrium. The response of the tissue to each dose of agonist was allowed to develop and plateau (about 3 minute per dose) prior to administration of the next higher dose. The rate was counted after 3 min. Immediately following the maximum increase in rate for the right atrium (chronotropic), and force for the left atrium (inotropic) were obtained. The antagonist was added to inhibit the agonist maximal response from 100 % to 20-30%. The ID_{50} values were calculated by plotting the increase (agonist) or the decrease (antagonist) in rate and tension of each agonist or antagonist from individual experiments as a percentage of their own maxima or minima. The right and left atrium tissues were washed and allowed to return to the resting rate, amplitude and basal frequencies (about 1 h). The buffer was changed every 20 minute during this period. The test compound (antagonist) was then added at the concentration which provided a ID_{35} to ID_{50} range and was incubated for 30 min. Following the 30 min incubation, another dose-response curve to isoproterenol dihydrochloride was obtained as described above. After maximal development of the final response, the tissues were washed and allowed to rest until the tissues returned to their resting rate and basal frequencies. Subsequent dose-response curves to isoproterenol dihydrochloride were carried out as described above using increasing concentrations of antagonist (in ID_{50}-ID_{80} range). The difference between the two concentrations of antagonist was usually a factor of ten. Normally three doses of antagonists could be used for the same tissue. ID_{50} values for the antagonists and each-dose response curve were established and the pA_2 value was calculated according to the method of Schild[462].

8.2.0.0.0 GUINEA-PIG TRACHEA CHAIN ASSAY (β_2).

The trachea assay was conducted at the same time as the experiment on heart. The throat from a guinea-pig described above was cut as near the head as possible. The trachea were dissected out, transferred to a dish containing HPSS solution and cut traversely between the segments of cartilage to obtain a number of rings of trachea muscle. These rings were freed of all fat tissue and blood vessel with extreme care to avoid stretching the ring. Several rings, usually 6, were sutured together, side by side, using polyester thread to form a chain, which was then mounted vertically in a HPSS solution water-jacketed bath (10 mL) at 37 °C that was aerated with 100% oxygen as illustrated in Fig. 16. The temperature was maintained by a constant temperature circulator (Haake Model E52). One end of thread was fixed to the bottom of the bath using rubber tubing to anchor the tissue and the upper end of each tracheal chain was connected to a force-displacement transducer (Grass FT03) under a resting tension of 0.25 g. Isometric tension was then recorded on a Grass polygraph (Model 7D). Following a 1 h equilibration period during which the physiological medium solution was changed every 15 min, cumulative dose-response curves for the agonist carbacol (carbamylcholine chloride) (increments of half-log units from 3×10^{-8} to 1×10^{-5} M) were prepared. The response of the tissue to each dose of carbacol was allowed to develop and plateau (about 5 minute per dose) prior to administration of the next higher dose. A constant level of tone was induced to achieve the maximum response. Following this, a cummulative dose-response curve to the agonist isoproterenol dihydrochloride (increments of half-log units from 10^{-9} to 3×10^{-6} M) was prepared to determine the ID_{50} value for the control curve. Subsequently, without washing, a cummulative dose-response curve to the antagonist were carried out to determine the ID_{50} value for the antagonist. The tissue was washed and allowed to return to the resting tension (about 1 h). The buffer was changed every 20 minute during this period. The test compound (antagonist) was then added at a concentration which provided 35 to 50% inhibition (ID_{35}-ID_{50} range) and incubated for 30 min. Following the 30 min incubation, another dose-response curve to carbacol was carried out as described above. After maximal development of the final response, a cummulative dose-response curve to the agonist isoproterenol dihydrochloride were established again to determine ID_{50} of INA in the presence of antagonist. The tisuue was washed and allowed to return to the resting tension (about 1 h). The buffer was changed every 15 minute during this period. Subsequent dose-response curves to isoproterenol dihydrochloride were carried out as described above using increasing concentrations of antagonist (in ID_{50}-ID_{80} range). The difference between the two concentrations of antagonist was usually a factor of ten. Normally three doses of antagonist could be used on the same tissue. ID_{50} values for the antagonists and each-dose response curve were established and pA_2 values were calculated using the method of Schild[462] described previously.

8.3.0.0.0 Materials

All chemicals used to prepare HPSS solution were purchased from Sigma. Carbachol and isoproterenol dihydrochloride were purchased from Aldrich. The novel dihydrochloride compounds were dissolved in HPSS solution. The novel free-base comppounds were first dissolved in DMSO to produce a 10^{-2} M solution and thereafter diluted with HPSS solution if possible. Test solutions were freshly prepared prior to use and placed them in an aluminum foil to protect them from light.

PART B

" HETEROCYCLIC 1,2-EPOXYALKAN-3-ONES AS CYTOTOXIC AGENTS"

1.0.0.0.0 INTRODUCTION.

1.1.0.0.0 NATURE OF CANCER.

Cancer is a common cause of death that is second only to cardiovascular ailments in incidence[467]. However, the treatment of cancer is much more difficult since it spreads rapidly and has a protracted course which results in a high incidence of mortality. The medical term for "cancer" or "tumor" is neoplasm which is defined as a hereditarily altered, relatively autonomous growth of tissues[468]. The proper use of this term includes both benign and malignant growths, although neoplasm is frequently interpreted as malignant. The critical difference between a benign and malignant neoplasm is that benign tumors do not metastasize, whereas malignant tumors do, A metastasis is a secondary growth originating from the primary tumor that starts to grow elsewhere in the body. Generally, the most common routes leading to the development of metastases are through the blood circulation and lymphatic system[469]. Certain significant cytological differences exist between cancer and normal cells and these differences are often very useful in the diagnosis of the disease[470,471]. For example, the size and shape of cancer cells are different and more variable than normal cells from the same tissue in morphology. Cancer cells undergo more rapid mitotic cell devision, the nucleus of cancer cells is often large with more apparent chromatin than normal cells, the ability to grow into adjacent tissues (invasiveness) is characteristic of cancer cells, and neoplastic transformation is accompanied by a wide variety of plasma membrane and cell surface changes[472].

1.2.0.0.0 CAUSE OF CANCER.

The majority of human cancers are probably induced by external environmental agents, acting singularly or in combination[473]. These include chemical carcinogens,[474] radiation energy,[474,475] and certain viruses[476,477] such as human T-cell leukemia virus, or HTLV, which are the only RNA tumor viruses (retrovirus) known to occur in man[478].

1.3.0.0.0 CANCER TREATMENT.

1.3.1.0.0 SURGERY.

Surgical excision is the oldest and the most extensively tested modality for the control of cancer. Although surgery can effectively remove a large tumor, it has limitations since surgical techniques are effective only for primary or regional lymphatic tumors. Non-operable disseminated neoplasms and microscopic tumor deposits present at the time of surgery ultimately induce further metastatic disease[479].

1.3.2.0.0 RADIATION.

The discovery of the X-ray by Roentgen, of radioactivity by Becquerel, and of radium by the Curies was promptly followed by the therapeutic application of these new techniques. In 1899 the first cancer, a basal cell epithelioma had been cured[480]. Radiation therapy is often superior to surgery, if it effectively destroys the tumor. Although there is minimal damage to the surrounding normal tissue, some side effects including anorexia, nausea, vomiting, diarrhea, esophagitis, skin reactions, mucosal reactions, epilation, and hematopoietic suppression[481] are often observed. Laser radiation has also been used for cancer therapy. The effect of dose, frequency of irradiation, and other conditions for most effective suppression of tumor growth have been investigated[482]. In clinical oncology, laser radiation is used to coagulate or excise tumor tissues *in situ*[483].

1.3.3.0.0 IMMUNOTHERAPY[484]

The concept that cancer patients may develop an immune response against their neoplasm is not new. Tummor immunology began in 1953 when Foley[485] and then in 1957 when Prehn and Main[486] conclusively demonstrated the presence of tumor specific antigens in methylcholanthrene-induced sarcomas in mice. Immunotherapeutic agents that stimulate host resistance to cancer may be described as nonspecific, active specific or passive immunotherapy agents. Nonspecific immunotherapy involves the use of agents such as BCG (bacillus calmette guerin) or Corynebacterium parrum, which are potent activators of multiple host defense mechanisms. Active specific immunotherapy studies to elicit specific antitumor immune responses by vaccination with tumor cells or tumor antigens have been carried out. Passive immunotherapy involving transfer of immune cells or antiserum with appropriate specificity to the patient may assist in suppressing tumor growth[487].

1.3.4.0.0 HYPERTHERMIA.

Tumors have been warmed to 42-43°C using ultrasound or microwaves. This approach to cancer therapy is still new and under experimental study[488].

1.3.5.0.0 CHEMOTHERAPY.

Cancer chemotherapy has been reasonably successful over the last four decades and now it has an established role to play in the treatment of many malignances. For example, the chemotherapeutic treatment of childhood acute lymphocytic leukemia (ALL) has been a major success. Choriocarcinoma, a neoplasm of the conceptus, was the first human cancer to be cured using methotrexate alone[489]. The first recorded clinical trial of a chemotherapeutic agent took place in 1942, when nitrogen mustard was administered to a patient with an advanced lymphosarcoma[490]. By 1950 the rate of introduction of useful new agents began to accelerate, and during the 1960's research in tumor cell biology and pharmacology led to more rational drug therapy[491]. In contrast to surgery and radiotherapy, the efficacy of chemotherapy is limited less by metastases, than the total mass of the tumor, since chemotherapy is usually not effective in destroying all cells in large tumors.

1.3.6.0.0 COMBINATION THERAPY.

Every effective therapeutic procedure elicits undesirable and at times dangerous side effects. The combination of radiation therapy with surgery, chemotherapy or immunotherapy or any combination thereof is now common practice[492-495].

1.4.0.0.0 ANTINEOPLASTIC AGENTS.

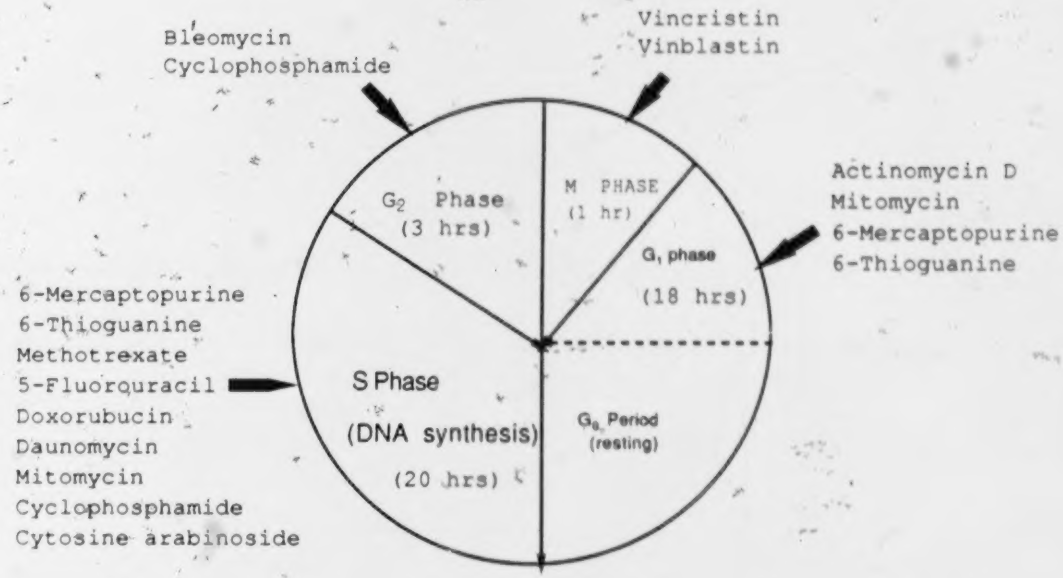
The major antineoplatic agents in use have been reviewed,[496] and classified on the basis of their chemical structure and mechanism of action. The following classes of commpounds are used in clinical cancer chemotherapy:[497,498] alkylating agents (nitrogen mustards, nitrosoureas), antimetabolites (cytarabin, 5-fluorouracil, methotrexate), antibiotics (actinomycin D, mitomycin C, doxorubicin, dactinomycin), vinca alkaloids (vincristin, vinblastin), miscellaneous drugs including various natural products (elipticines[499]), enzymes (l-asparginase), and cis-platinum[500], which is the most exciting antineoplastic drug that has entered general clinical practice in a number of years (inorganic complex), as well as a number of non-platinum antitumor metal complexes including Rhodium I, Iridium I and Ruthenium[501].

1.4.1.0.0 CANCER DRUGS AND CELL CYCLE.

The cell cycle consists of four phases, which are related to DNA synthesis and mitosis[502]. Certain interesting features of this cycle have been reviewed[503,504]. Many of the effective cancer chemotherapeutic drugs exert their action on cancer cells as they pass through the cell cycle. Certain drugs are effective only during specific phases of the cell cycle, such as the S phase of cellular synthesis, called cycle- or phase-specific, whereas others are relatively independent of the cycle which are known as cycle- or phase-nonspecific[505] (Fig. 26).

1.4.2.0.0 SELECTIVE TOXICITY.

The clinically useful antineoplastic agents exhibit a greater toxicity toward sensitive malignant cells than normal cells of the tumor-bearing host. They are considered to exhibit selective toxicity. The most useful chemotherapeutic agents appear to act by affecting enzymes or subtrates that are acted upon by enzyme systems. For most agents, the target is an enzyme or substrate that is related to DNA synthesis or function,[506] and consequently, these drugs exert their major toxic and antitumor effects by inhibiting cells that undergo DNA synthesis at some time in their life cycle. The mechanism and sites of action of selected drugs that are useful in the treatment of the neoplastic diseases are given in Table 40[507]. Some new developments on the mechanism of action of anticancer drugs[508] and specific antitumor antibiotics[509] have been reviewed. Most antineoplastic agents are toxic and non-selective.


Bleomycin
Cyclophosphamide
Vincristin
Vinblastin
Actinomycin D
Mitomycin
6-Mercaptopurine
6-Thioguanine
M PHASE
(1 hr)
G_2 Phase
(3 hrs)
G_1 phase
(18 hrs)
6-Mercaptopurine
6-Thioguanine
Methotrexate
5-Fluorouracil
Doxorubucin
Daunomycin
Mitomycin
Cyclophosphamide
Cytosine arabinoside
S Phase
(DNA synthesis)
(20 hrs)
G_0 Period
(resting)

G_2 phase: Time gap between DNA synthesis and mitosis

G_1 phase: Time gap between mitosis and DNA synthesis

Fig.26 Phase-specific cancer drugs are effective only at certain stages in the cell cycle. During the G_0 period, none of the chemotherapeutic agents are particularly effective. Some agents are useful at more than one stage.

Table 40. Summary of the mechanisms and sites of action of selected drugs used in cancer chemotherapy[507].

Site of action	Drug	Mechanism of action
Purine synthesis	Methotrexate	Inhibits one-carbon transfer required for purine ring synthesis.
	6-Mercaptopurine and 6-thioguanine	Inhibit purine ring synthesis.
	Hydroxyurea	Inhibits ribonucleotide reductase
Pyrimidine synthesis	Fluorouracil	Inhibits dTMP formation by blocking thymidylate synthetase
	Azaribine	Inhibits UMP formation
DNA polymerase	Cytarabine	Competitively inhibits incorporation of dCTP into DNA
DNA (direct interaction)	Alkylating agents	React covalently with DNA, often cross-linking the strands
	Bleomycin	Damages DNA and prevents repair
	Doxorubicin, Daunorubicin, and Actinomycin D	Intercalation into DNA
	Mithramycin	Non-intercalative binding to DNA to inhibit nucleic acid synthesis
Protein synthesis	L-Asparaginase	Deaminates asparagine, starving the cell for this amino acid
Protein function	Vinca alkaloids	Disrupt microtubes, producing metaphase arrest

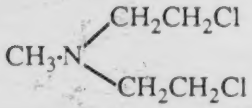
Undesirable side effects result from their use as listed in Table 41[510]. The search for new approaches to the discovery and development of more specific and less toxic antineoplastic agents are being investigated[511].

1.5.0.0.0 ALKYLATING AGENTS AND THEIR CHEMICAL MODE OF ACTION.

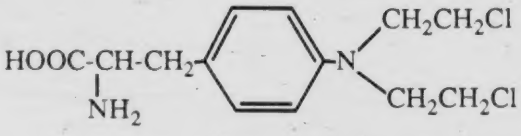
Alkylating agents, which were the first clinically useful compounds employed to treat patients with malignancies, are still the most widely utilized class of antineoplastic drugs[506]. There are six major chemical classes of alkylating agents (See structures in Fig.27) 1) nitrogen mustards (mechlorethamine, melphalan), 2) nitrosoureas (semustine, carmustine), 3) methanesulfonic acid esters (busulfan), 4) triazenes (decarbazin), 5) ethylenimines (aziridines) and 6) epoxides [dianhydrogalactitol, epipropidine (eponate), epoxypiperazine, etoglucid (epodyl)[512] and crotepoxide[513]]. Most alkylating agents are highly reactive, since the formation of a highly reactive electrophilic alkyl cation (RC^+H_2, carbonium ion) can react with the ionized carbonyl groups of amino acids and proteins, the ring nitrogen of histidine, the ionized primary and secondary hydroxyl groups of phosphoric acid and the oxygen atoms at position four and six of thymine and guanine[514].

Table 41. CLINICALLY UNDESIRABLE SIDE EFFECTS OF ANTICANCER DRUGS[510].

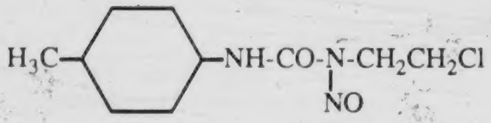
Tissue or system affected	Toxic effects
Bone marrow	Leukopenia and lymphocytopenia with an increased risk of infection or activation of quiescent infection. Immunosupression. Thrombocytopenia leading to hemorrhage. Anemia.
Digestive tract	Oral ulceration Intestinal ulceration, diarrhea
Hair root	Alopecia.
Gonads	Menstrual irregularities, amenorrhea, infertility. Impaired spermatogenesis, sterility.
Tissue undergoing repair (surgical wounds, etc.)	Impaired healing.
Tumor mass	In the case of leukemias and lymphomas rapid destruction of the tumor mass can result in the release of large amounts of nucleic acid breakdown products, and a consequent increase in uric acid can cause renal damage.
Fetus	Teratogenesis



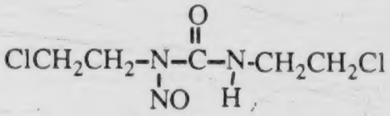
Mechlorethamine



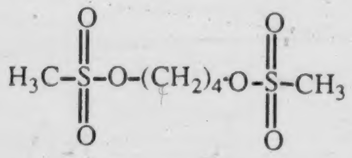
Melphalan (L-PAM)



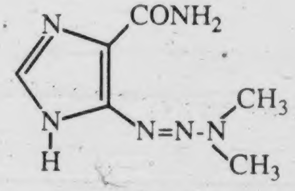
Semustine (Methyl-CCNU)



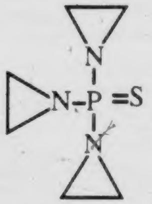
Carmustine (BCNU)



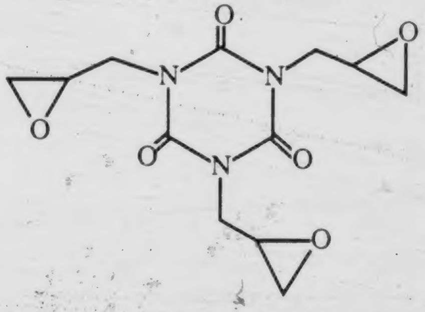
Busulfan (myleran)



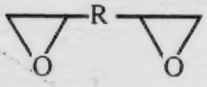
Dacarbazin



Thio-TEPA

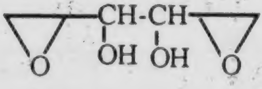


1,3,5-Triglycidyl-s-tri-azintrio

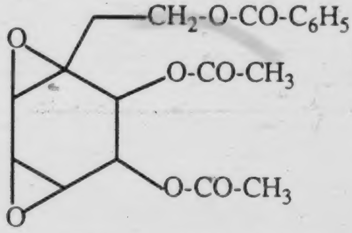


R= (a)-$(CH_2)n$-

R= (b)-$(CHOH)_2$



Dianhydrogalactitol



Crotepoxide

Fig.27. Representative alkylating antitumor agents.

1.5.1.0.0 MECHANISM OF ACTION OF ALKYLATING AGENTS.

1.5.1.1.0 NITROGEN MUSTARDS.

A typical proposed mechanism of action for mechlorethamine (a nitrogen mustard)[515] is shown in Fig.28. In neutral and alkaline aqueous solution, a chloride ion (Cl^-) is liberated from one of the chloroethyl side chains with subsequent internal cyclization to give the biologically active immonium ion intermediate. This strained three-membered ring can open to give a carbonium ion which alkylates the nitrogen at position seven of the guanine residue of nucleic acids. The second chloroethyl group can also undergo cyclization and subsequent reaction with another nucleophile or guanine as shown in Fig.28. This sequence of reactions can produce breaks in the DNA molecule and cross-linking of its twin strands. This process interferes with DNA replication (due to altered base pair formation of the alkylated guanine with thymine), RNA transcription and ultimately preventing cell division.

1.5.1.2.0 MECHANISM OF ACTION OF NITROSOUREAS.

The nitrosoureas are groups of lipophilic alkylating agents that can cross the blood brain barrier and are used to treat brain tumors. Nitrosoureas undergo extensive biotransformation *in vivo*, producing a variety of biologic effects, including alkylation, carbamoylation and inhibition of DNA repair[516]. The chloroethylnitrosoureas were among the first anticancer drugs to be studied by DNA filter elution methods.

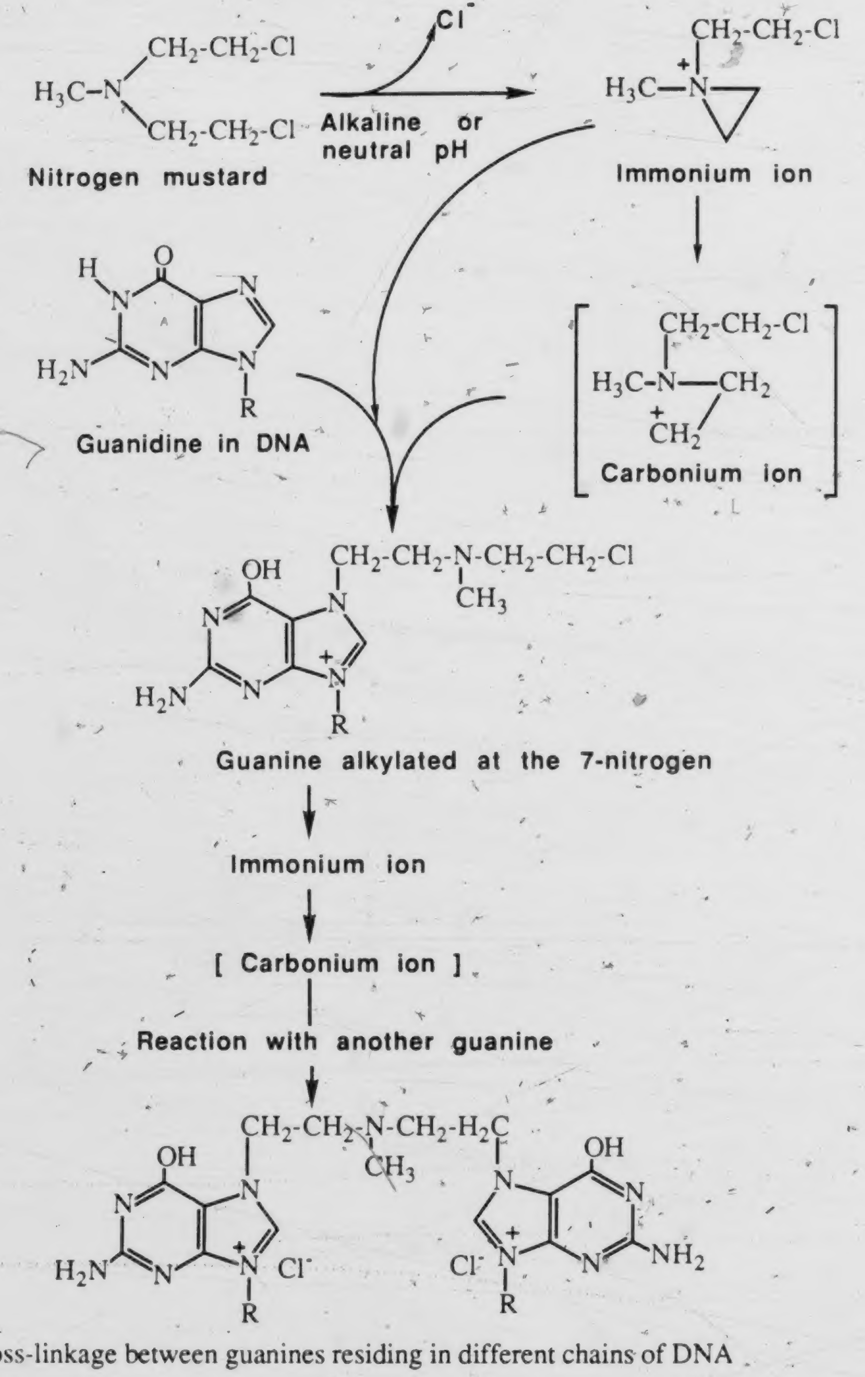

Cl⁻
Alkaline or neutral pH
Nitrogen mustard
Immonium ion
Guanidine in DNA
Carbonium ion
Guanine alkylated at the 7-nitrogen
Immonium ion
[Carbonium ion]
Reaction with another guanine
Cross-linkage between guanines residing in different chains of DNA

Fig. 28. The mechanism by which nitrogen mustard is covalently bonded to the 7-nitrogens of two guanine residues.

The mechanism[517] of their proposed action is illustrated in Fig.29.

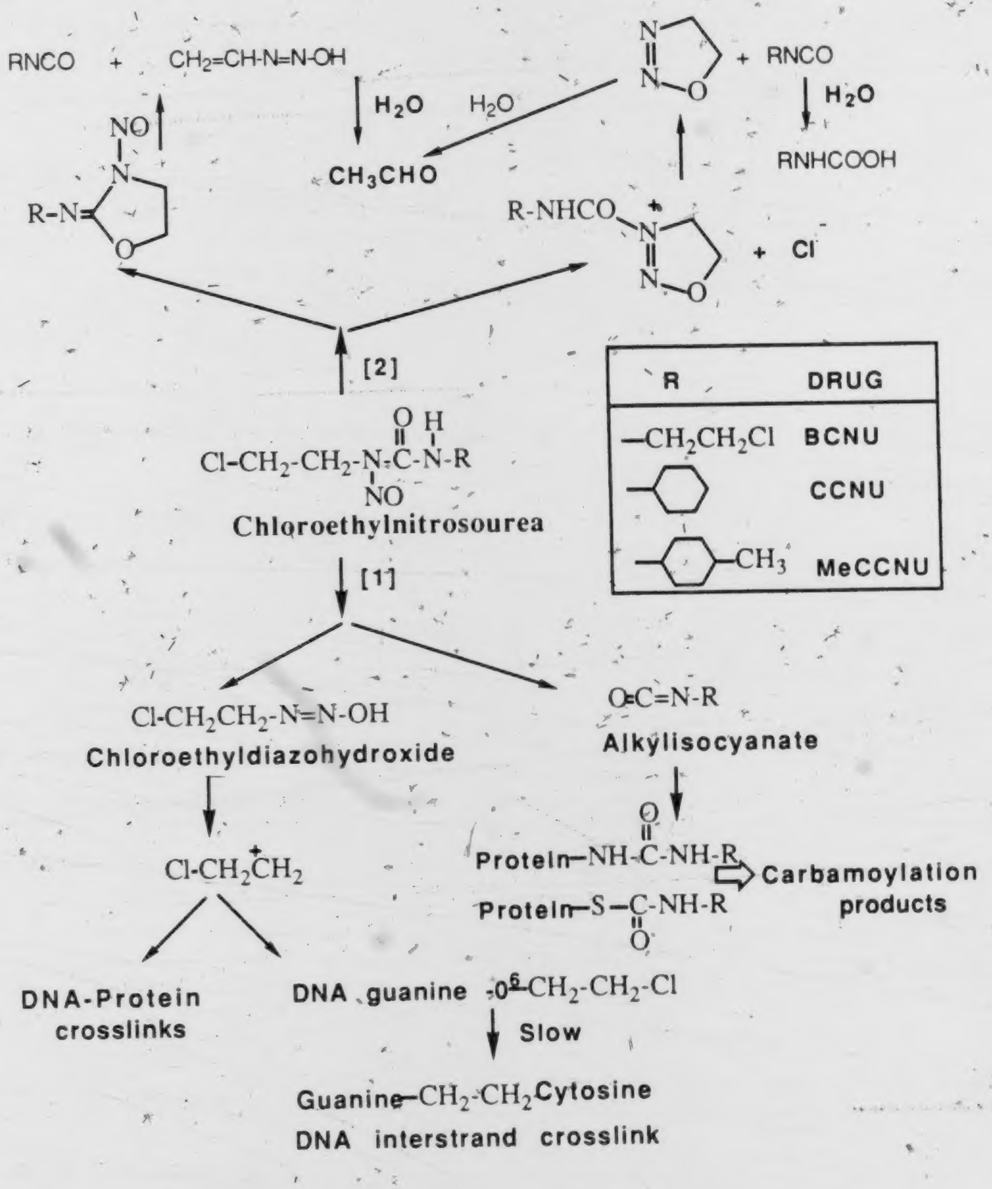
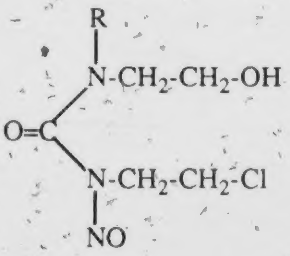

RNCO + CH2=CH-N=N-OH
H2O
H2O
CH3CHO
+ RNCO
H2O
RNHCOOH
NO
R-N=
R-NHCO
+ Cl
[2]
Cl-CH2-CH2-N-C-N-R
NO
Chloroethylnitrosourea
R
DRUG
—CH2CH2Cl
BCNU
CCNU
CH3
MeCCNU
[1]
Cl-CH2CH2-N=N-OH
Chloroethyldiazohydroxide
O=C=N-R
Alkylisocyanate
Cl-CH2CH2
Protein—NH-C-NH-R
Protein—S—C-NH-R
Carbamoylation products
DNA-Protein crosslinks
DNA guanine -O6-CH2-CH2-Cl
Slow
Guanine—CH2-CH2-Cytosine
DNA interstrand crosslink

Fig. 29 Reaction paths and products of chloroethylnitrosourea.

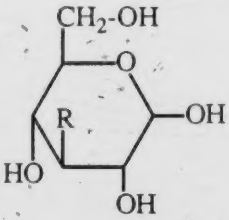
Chloroethylnitrosoureas such as BCNU, CCNU, and MeCCNU decompose spontaneously to give two types of highly reactive compounds that engage in two different types of addition reactions: alkylation and carbamoylation (Fig.29).

Alkylation reactions derive from the chloroethyl diazohydroxide **[1]** which adds a chloroethyl group to various sites on nucleic acids, proteins and the guanine-O^6 position; and from **[2]** where two possible cyclic intermediates can add a hydroxyethyl group to these sites[518]. The carbamoylation reactions evolving from alkylisocyanates do not contribute to antitumor activity. Nitrosourea antineoplastic drugs have been reviewed[519]. A new class of very potent nitrosoureas (**1**) and a chlorozotocin analog (**2**), possess β-hydroxy groups that activate the molecule nonenzymatically by intramolecular cyclization without the generation of an isocyanate moiety. These compounds possess a therapeutic ratio 3-5 times greater than that of CCNU toward L1210 leukemia in mice[520].



1

R= Alkyl



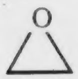
2

R=NHCO-N-CH$_2$-CH$_2$-Cl with NO on N

1.6.0.0.0 EPOXIDES.

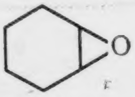
1.6.1.0.0 NOMENCLATURE.

Three-membered ring systems containing oxygen can be regarded as derivatives of ethylene oxides or 1,2-epoxides (**3**). The nomenclature of epoxides is somewhat confusing. For example, the ethylene oxide (**4**) is often referred to as an epoxyethane or oxirane derivative, a cyclohexane derivative or 7-oxabicyclo[4.1.0]heptane. In addition, several simple epoxides have been given trivial names such as epichlorohydrin (**5**), and glycidic acid (**6**).



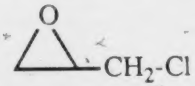
3

Ethylene oxide



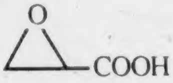
4

Cyclohexene oxide



5

Epichlorohydrin

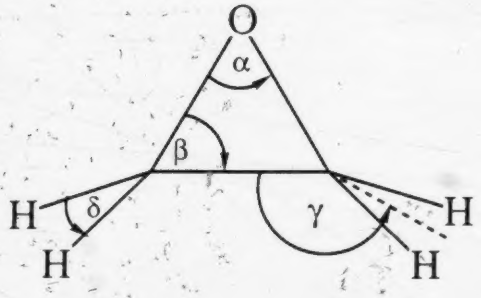


6

Glycidic acid

1.6.2.0.0 PHYSICAL PROPERTIES OF OXIRANES.

The bond lengths and bond angles present in oxirane have been obtained primarily by microwave spectroscopy, electron diffraction, and more recently, the NMR spectrum in the liquid-crystal phase[521]. The geometric data of oxirane determined from the various procedures[521] are summarized in Table 42[522]. All of the measurements clearly show that the plane of the hetero-ring is perpendicular to the plane defined by the four hydrogen atoms. The two carbon atoms of the ring are symmetrically located above the plane of the four hydrogen atoms.



	Reference[522]				
	a	b	c	d	e
C-C	1.54	1.472	1.4728	1.47	1.483
C-O	1.43	1.436	1.4363	1.44	1.433
C-H	1.05	1.082	1.0802	1.08	1.088
α	67°	61°24'	61°41'	61°24'	62.3°
β	57°26'	59°18'	59°9'	59°18'	58.85°
γ	-	159°25'	158°5'	158°6'	155.3°
δ	117°28'	116°41'	116°51'	116°15'	114.5°

Table 42. Geometric data for the oxirane ring measured by different methods. The letters a-c refer to the reference numbers 522 a-e.

The C-C bond length is intermediate between those for a single (1.54 Å) and a double (1.33 Å) bond; similarly, the H-C-H bond angle lies between tetrahedral (109°28') and trigonal (120°) bonding[522]. The same situation is observed for the C-C-C bond angle in the case of substituted oxiranes[521].

1.6.2.1.0 IR SPECTROSCOPY OF OXIRANES.

Oxirane exhibits three intense IR bands[523,524] at 1265, 1165 and 865 cm^{-1}. The latter band is due to the asymmetrical ring-stretching vibration. A band at 1250 cm^{-1} is characteristic for the oxirane ring[525]. This band is usually attributed to the symmetrical stretching vibration and is present in both *cis*- and *trans*-oxiranes. *cis*-Oxiranes are further characterized by absorptions between 829 and 838 cm^{-1}, and *trans*-oxiranes by a band between 882 and 917 cm^{-1}.[526] The IR and Raman spectra of alkyl-substituted oxiranes have been reported[527] and are the subject of a review[528].

1.6.2.2.0 NMR SPECTRA OF OXIRANES.

The NMR spectra of the three-membered heterocycles display resonances which are of great value in structure assignment. The proton chemical shifts for various substituted oxiranes are reported in a number of reviews and handbooks[529,530,531]. Mortimer[532] has determined the coupling constants for the three-membered heterocyclic ring systems shown in Table 43. *cis*-Vicinal coupling constants are generally larger than the corresponding *trans* coupling constants[533]. This is in contrast to large rings, where $J_{trans} > J_{cis}$[531]. The magnitude of J_{gem} and J_{vic} coupling constants depend more on the number of non-bonding electron pairs at the heteroatom than on its electronegativity[534] as illustrated in Table 43.

	J_{cis}	J_{trans}	J_{gem}
Oxirane	4.45	3.1	5.5
Thiirane	7.15	5.65	0.4
Aziridine	6.3	3.8	2.0

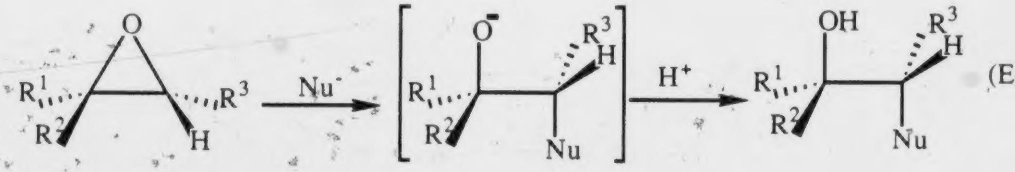
Table 43. Proton coupling constants for three-membered heterocyclic rings.

1.6.3.0.0 CHEMICAL PROPERTIES.

The mechanism for the opening of the epoxide ring can be considered under three headings: a) orientation of ring opening b) stereochemistry and c) kinetics of ring opening.

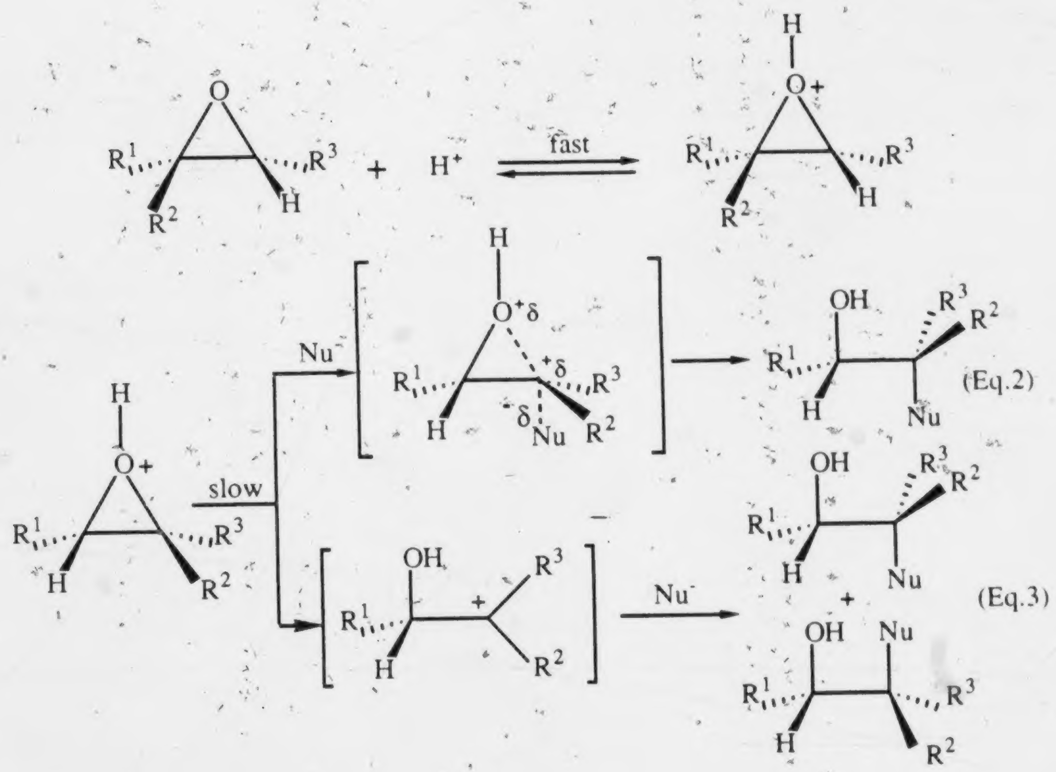
1.6.3.1.0 ORIENTATION OF RING OPENING INVOLVING THE C-O BOND.

Oxiranes undergo facile ring-opening upon reaction with nucleophilic reagents which is attributed to ring strain and the basic nature of the oxygen atom in the heterocycle[535]. The reaction of oxiranes with nucleophiles to form C-C, or C-X where X= N,O,S,Se or Te, bonds is facilitated by electrophilic assistance from protic solvents or Lewis acids[536,537]. The mechanism of oxirane ring-opening with respect to regio- and stereoselectivity of oxiranes has been reviewed[536,538,539]. The opening of oxiranes by reaction with nucleophiles in basic or neutral conditions, usually involves an S_N2 mechanism. For asymmetric oxiranes, attack by nucleophiles generally takes place with inversion at the least-substituted carbon atom (Eq.1).



(Eq.1)

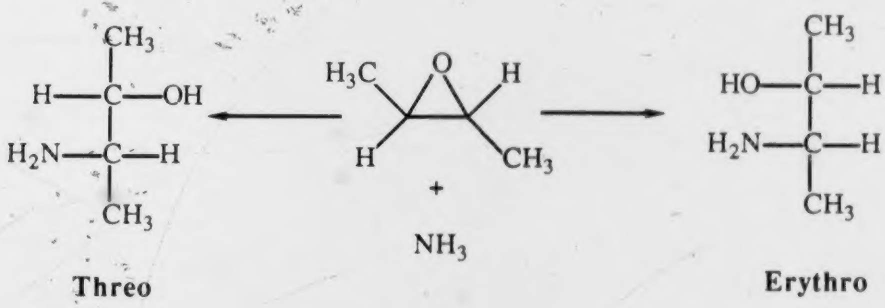
In acidic medium, the first step is the pre-equilibrium addition of a proton to oxygen. An oxonium ion is formed that can react further either by a S_N2 (Eq.2) or S_N1 (Eq.3) mechanism.



Nucleophilic attack proceeds via a transition state (Eq.2) where both bonds are longer than usual (borderline S_N2), and the configuration of the carbon at which the nucleophile attacked is inverted[540]. In the S_N1 mechanism (Eq.3), which favors tertiary carbons, nucleophilic attack occurs at the more highly substituted carbon. However, even when protonated epoxides react by the S_N2 mechanism, attack is usually at the more highly substituted carbon which occurs with inversion of configuration[541]. When the substituent at the most substituted carbon atom is phenyl or vinyl, a stablized carbonium ion may be formed resulting in a S_N1 mechanism[70] (Eq 3). Thus, it is often possible to change the direction of ring opening by changing the reaction conditions from basic to acidic or vice versa. When an epoxide ring is fused to a cyclohexane ring, S_N2 ring-opening invariably affords diaxial rather than diequatorial ring-opened products[542]. According to Krassusky's rule,[543,544] the opening of oxirane involving nucleophilic attack at the least substituted carbon is defined as "normal opening" whereas, opening involving attack at the more substituted carbon is defined as "abnormal opening". Under basic or neutral conditions, the isomer produced by "normal opening" is usually the major product[544]. This provides strong evidence for an S_N2 mechanism.

1.6.3.2.0 STEREOCHEMISTRY OF RING OPENING.

With certain epoxides, the products obtained upon reaction with nucleophiles can be two stereoisomers. Thus, reaction of ammonia with *trans*-2,3-epoxybutane can yield either *erythro-* or *threo*-3-amino-2-butanol (Eq.4).



(Eq.4)

In fact, only the *erythro* isomer is formed due to inversion of configuration at the point of attack which is the expected result of an S_N2 mechanism[545].

1.6.3.3.0 KINETICS OF RING OPENING.

The kinetics of a considerable number of ring-opening reactions of epoxides have been studied. Kinetic studies covering a range of epoxides have been carried out in basic or neutral solution for the reactions with ammonia and various amines in aqueous amine solvents[546], thiocyanate ion,[547] nitrate ion,[548] thiosulfate ion in aqueous acetone,[549] and thiosulfate ion in aqueous ethanol[550]. Barlett and Ross[551] have shown that all these reactions proceeded via a S_N2 mechanism.

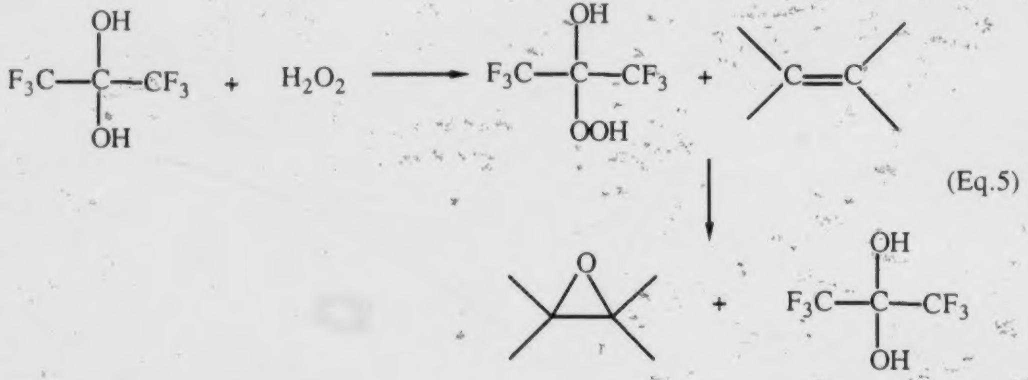
1.7.0.0.0 PREPARATION OF OXIRANES.

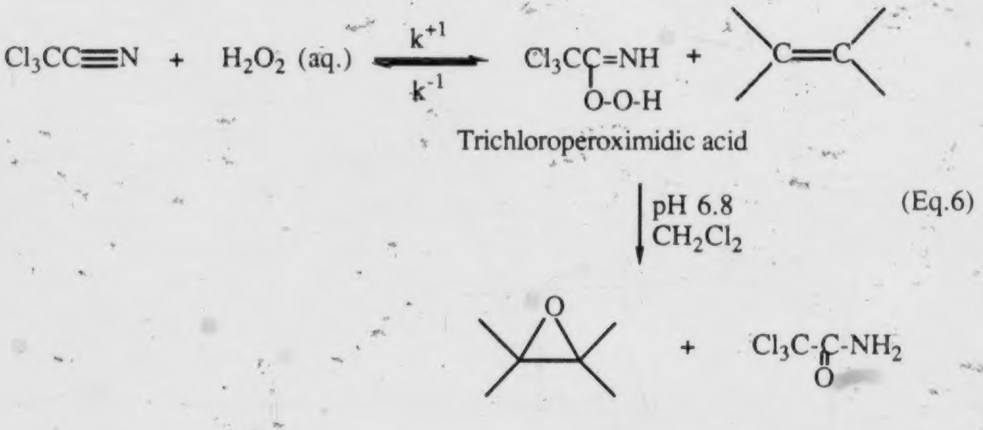
Ethylene oxide (**1**), the parent epoxide, was first prepared in 1859 by the French chemist A. Wurtz who recognized it was a "cyclic ether". The importance of oxiranes as intermediates in organic synthesis is well-documented[552,553]. Epoxides can be synthesized by a variety of methods.

1.7.1.0.0 SYNTHESIS OF OXIRANES FROM ALKENES AND ARENES.

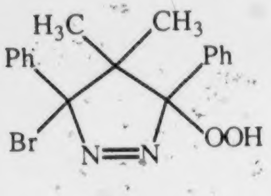
Oxiranes are typically prepared from alkenes on a laboratory scale by reaction with organic peroxides in the presence of a metal catalyst [t-butylhydroperoxide (TBHP) in the presence of $Mo(CO)_6$ catalyst][553] or by a variety of peroxy acids[552,554] such as *meta*-chloroperbenzoic acid (MCPBA)[555] or trichloroperoxyimidic acid[556] (Eq.6) which are used for alkene epoxidations on a molar scale. Peroxytrifluoroacetic acid,[557] one of the most electrophilic peroxyacids is used for the epoxidation of electron deficient olefins, but it suffers the disadvantage of having to be prepared *in situ* by the reaction of trifluoroacetic anhydride with

90% hydrogen peroxide. The resulting solution is highly acidic and can have deletorious effects upon the yield of epoxide. A convenient alternative to peroxytrifluoroacetic acid is 3,5-dinitroperbenzoic acid which can be stored for an extended period of time[558]. Alkenes can also be epoxidized with H_2O_2 in contact with basic alumina (alumina/H_2O_2)[559] or in the presence of one of the following catalysts: *ortho*-nitrophenylselenic acid, 2,4-dinitrophenylselenic,[560] hexafluoro-acetone hydrate (Eq.5),[561] tetrachloroacetone,[562] arsonated polystyrene resins,[563] and trichloroacetonitrile in a neutral biphasic solvent system (Eq. 6)[556].


(Eq.5)


(Eq.6)

Some other reagents which are suitable for the epoxidation of alkenes are 3-bromo-3-phenyl-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3-H-pyrazol (**7**),[564] N-benzoylperoxycarbamic acid (**8**),[565] the 2-benzensulfonyl-3-aryloxaziridine (**9**)[566] and peroxycarboximidic acid (**10**)[567].



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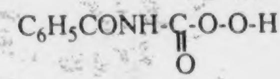
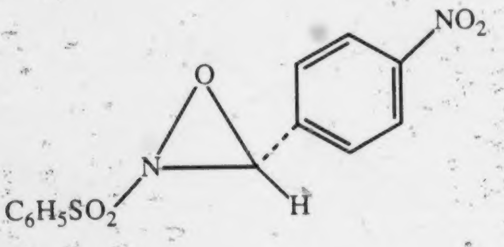


$C_6H_5CONH\text{-}\underset{\underset{O}{\|}}{C}\text{-}O\text{-}O\text{-}H$

8



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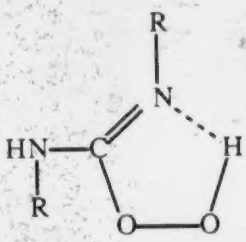
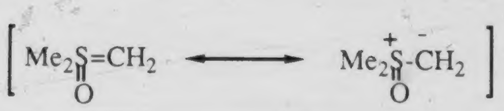


10

1.7.2.0.0 SYNTHESIS OF OXIRANES VIA CARBONYL ADDITIONS.

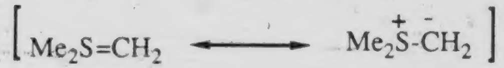
1.7.2.1.0 SULFUR YLIDES.

The synthesis of oxiranes via condensation of aldehydes or ketones with sulfur ylides has become an important synthetic technique[568]. Dimethyloxosulfonium methylide (**11**) and dimethylsulfonium methylide (**12**) react with ketones to afford oxiranes[569] via a methylene transfer reaction (Eq.7).



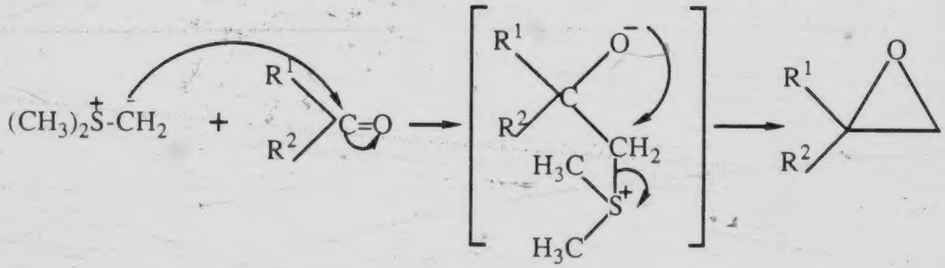
$$\left[\mathrm{Me_2}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{S}}\mathrm{=CH_2} \longleftrightarrow \mathrm{Me_2}\overset{+}{\underset{\overset{\|}{\mathrm{O}}}{\mathrm{S}}}\mathrm{-}\overset{-}{\mathrm{C}}\mathrm{H_2}\right]$$

11



$$\left[\mathrm{Me_2S=CH_2} \longleftrightarrow \mathrm{Me_2}\overset{+}{\mathrm{S}}\mathrm{-}\overset{-}{\mathrm{C}}\mathrm{H_2}\right]$$

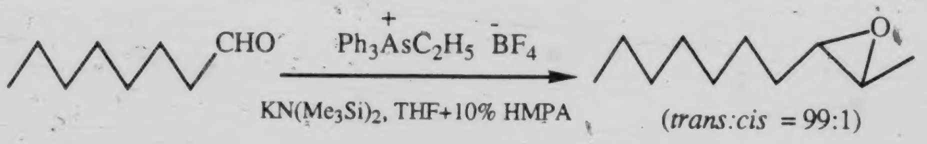
12


$(CH_3)_2\overset{+}{S}-\overset{-}{C}H_2$
+
R^1
R^2
C=O
R^1
O^-
C
R^2
CH_2
H_3C
S^+
H_3C
R^1
O
R^2

(Eq.7)

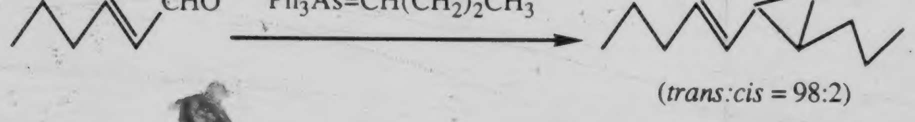
1.7.2.2.0 ARSONIUM YLIDES.

A number of aldehydes react cleanly with arsonium ylides to yield *trans*-oxiranes with stereoselectivity ≥50:1 as illustrated in equations 8 and 9. The stereoselectivity is dependent upon the arsonium salt counterion[570].


CHO
$Ph_3\overset{+}{As}C_2H_5\ \overset{-}{B}F_4$
$KN(Me_3Si)_2$, THF+10% HMPA
O

(*trans:cis* = 99:1)

(Eq.8)


CHO
$Ph_3As=CH(CH_2)_2CH_3$
O

(*trans:cis* = 98:2)

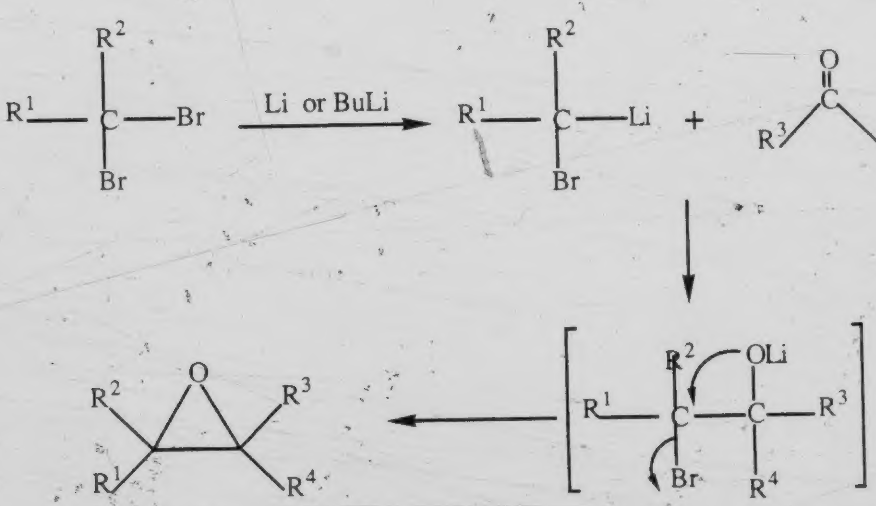
(Eq.9)

1.7.2.3.0 DIAZOALKANES.

Aldehydes and ketones can also be converted to epoxides by treatment with a diazoalkane, most commonly diazomethane, but an important side reaction is the formation of an aldehyde and ketone with one more carbon than the starting compound[571].

1.7.2.4.0 GEM-DIHALIDES.

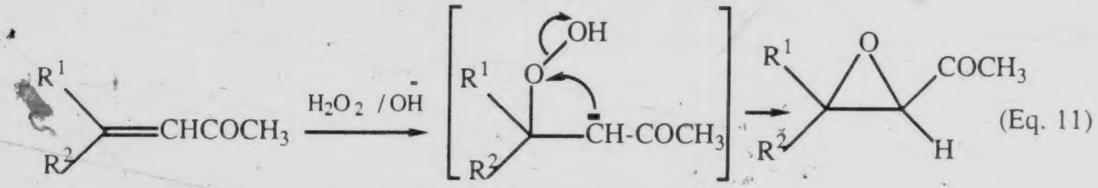
Gem-dihalides upon reaction with a carbonyl compound and Li or BuLi give epoxides[572] (Eq.10).



(Eq. 10)

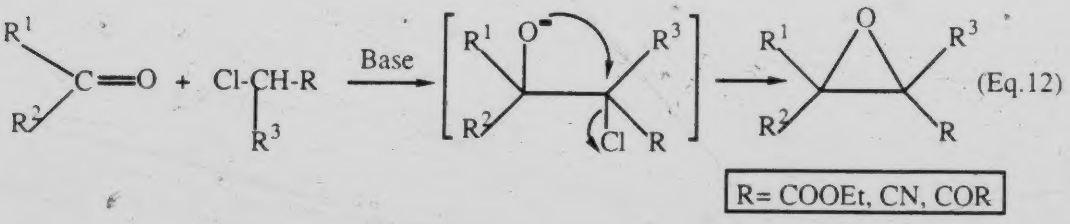
1.7.2.5.0 OXIRANES FROM α,β-UNSATURATED KETONES.

α,β-Unsaturated ketones react with H_2O_2 and alkali to give α,β-epoxyketones[573] (Eq.11).


R1
R2
CHCOCH3
H2O2 / OH
OH
O
CH-COCH3
COCH3
H
(Eq. 11)

1.7.2.6.0 OXIRANES FROM α-HALOESTERS, NITRILES, KETONES.

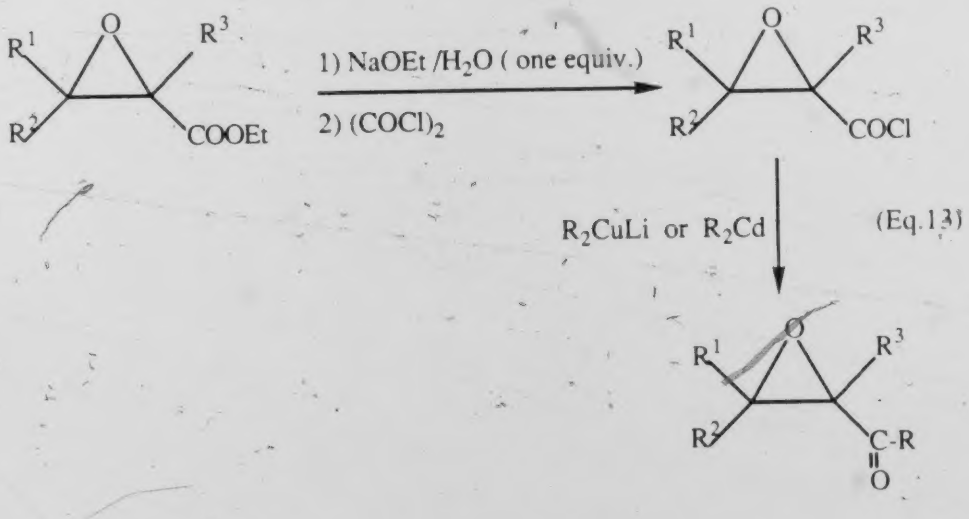
Aldehydes and ketones, upon condensation with α-haloesters, nitriles or ketones in the presence of bases, in an anhydrous organic solvent or liquid ammonia,[574] yield the respective α,β-epoxyesters, nitriles or ketones. This reaction is called the Darzen's condensation[575] (Eq.12). The reaction involves an initial Knoevenagel-type condensation (aldol condensation),[576] followed by an internal S_N2 reaction[577].


R1
R2
C=O
+
Cl-CH-R
R3
Base
O
Cl
R
(Eq.12)
R= COOEt, CN, COR

1.7.3.0.0 SYNTHESIS OF β-SUBSTITUTED α,β-EPOXYKETONES.

1.7.3.1.0 FROM α,β-EPOXYACYLCHLORIDES USING ORGANOMETALLIC REAGENTS.

α,β-Epoxyacyl chlorides,[578] synthesized from epoxyesters using the Claisen reaction, react cleanly and under mild conditions with lithium dialkylcopper reagents to give high yields of α,β-epoxy ketones[579]. Another type of organometallic reagent that gives good yields of α,β-epoxyketones upon treatment with acyl halides are organocadmium reagents R_2Cd (Eq.13).



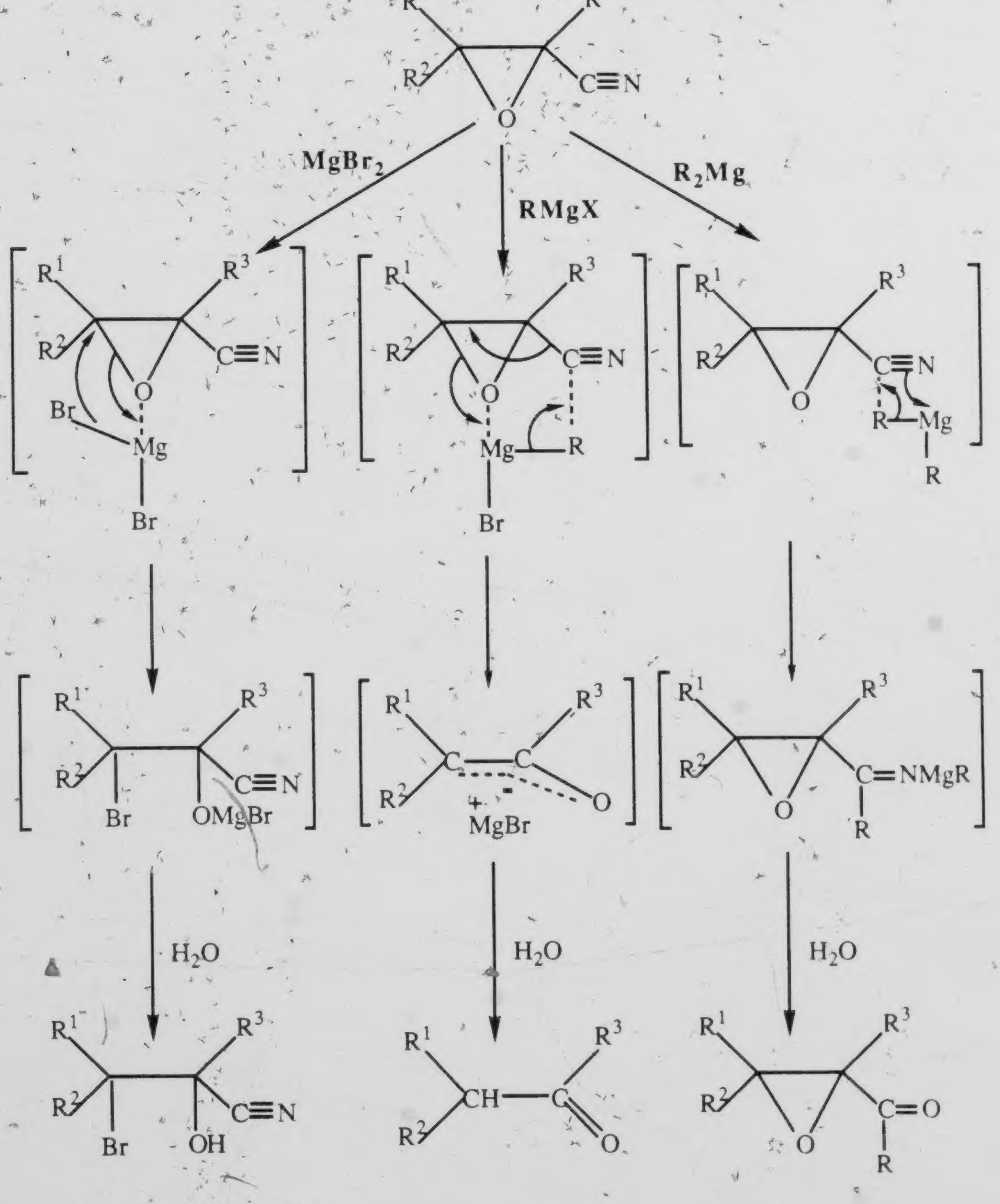
(Eq.13)

1.7.3.2.0 SYNTHESIS OF KETONES FROM ESTERS, ANHYDRIDES OR AMIDES USING ORGANOMETALLIC REAGENTS.

Anhydrides and esters give tertiary alcohols when treated with Grignard reagents. At low temperature,[580] the solvent HMPT[581] and inverse addition have been used to increase the yield of ketones. Amides give better yields of ketones at room temperature, but the yield is still only in the 10 to 50% range.

1.7.3.3.0 OXIRANES FROM α,β-EPOXYNITRILES USING ORGANOMETALLIC REAGENTS.

α,β-Epoxyketones can also be synthesized from the reaction of α,β-epoxynitriles with organometallic reagents (R_2Mg),[582] or with alkylithiums[583]. The oxirane ring in both cases is maintained (Eq.14) Other organometallic reagents such as $MgBr_2$ and RMgX react with α,β-epoxynitriles by different mechanisms (Eqs. 15 and 16) to afford different products[584].


MgBr$_2$
RMgX
R$_2$Mg
H$_2$O
H$_2$O
H$_2$O

(Eq. 16) (Eq. 15) (Eq. 14)

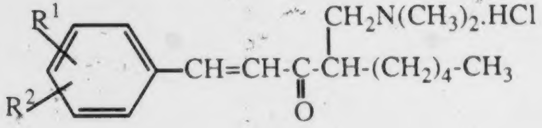
2.0.0.0.0 OBJECTIVES OF RESEARCH.

α,β-Unsaturated ketones have been classified as alkylating agents based on their ability to undergo addition reactions (Michael reaction) with biologically important cellular nucleophiles. There has recently been a considerable degree of pharmacological interest in 3,3'-diacetoxy-α,β-dialkylstilbenes and their corresponding oxides, α,β-epoxysulfoxides and methenomycins. All of these compounds contain an oxirane ring system that is activated by an electron-withdrawing substituent such as phenyl, sulfonyl or carbonyl. Activated oxiranes that react readily with cellular nucleophiles and exhibit significant cytotoxic activity are potientially useful antineoplastic agents. The synthesis of activated *cis*- and *trans*-1-[1-oxido-2-(3-,4-)pyridinyl]-2-methyloxiranes, methyl 3-[1-oxido-2-(3-,4-pyridinyl)]-2,3-epoxypropanoates, and their reaction with sulfur, oxygen and nitrogen nucleophiles were previously investigated in this research group. Although these activated oxiranes react readily with model nucleophiles, they were inactive in the P388 Lymphocytic leukemia screen. This lack of antineoplastic activity is likely due to their failure to act as biological alkylating agents. The objectives of this study were i) to synthesize a new class of activated 1-(2-pyridinyl)-2-alkylcarbonyloxiranes; and ii) to determine their structure-activity relationships (SARs) using the P388 Lymphocytic leukemia screen with particular emphasis on the stereochemistry of substituents (*cis* or *trans*) and the length of the alkyl group (lipophilicity).

3.0.0.0.0 RESULTS AND DISCUSSION.

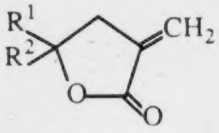
3.1.0.0.0 RATIONALE FOR THE PRESENT INVESTIGATION.

Alkylating groups have been attached to many types of molecules among which heterocyclic compounds are well represented. The design of activated alkylating agents, that react with cellular nucleophiles such as L-cysteine, glutathione or sulfohydryl-containing enzymes can be used as a model to develop new classes of cytotoxic drugs[585] such as Mannich bases[586-588] (**13**), α-methylene-γ-lactones[589] (**14**) and N-(3-oxoprop-1-enyl)pyrimidines[590] (**15**). The antineoplastic activity of compounds containing an α,β-unsaturated moiety has been attributed to their reaction with cellular nucleophiles[591-593]. Nucleophilic attack at the β-position of α,β-unsaturated carbonyl compounds is known as the Michael reaction, and it has been studied extensively primarily due to its synthetic usefulness[586]. A number of compounds, which can be conceived as prodrugs to putative alkylating species, have been developed by Sartorelli and coworkers. Thus, the antineoplastic activity of arylsulfonylhydrazones of 2-formylpyridine N-oxide[594-596] (**16**) has been attributed to the potent alkylating species 1-oxidopyridin-2-yldiazomethane[597,598] (**17**). Activity was retained when the pyridine N-oxide moiety was replaced by pyridazine N-oxide. However, replacement of the pyridine N-oxide moiety by benzene, quinoline N-oxide, isoquinoline N-oxide, or pyrimidine N-oxide resulted in a complete loss of antineoplastic activity. α,β-Epoxysulfoxides (**18**) react readily with nucleophiles. The β-carbon of (**18**) is highly reactive to nucleophiles yielding dialkyl ketones or aldehydes in high yield under mild conditions[599-600]. 3,3'-Diacetoxy-α,β-dialkylstilbene oxides (**19**) exhibit strong mammary tumor-inhibiting effects[601]. The oxirane moiety was found to be the most common functional group present in compounds with 12 or less carbon atoms that exhibited antitumor activity[602] (Table 44). Oxiranes also have other important biological roles. Leukotriene A_4 (LTA_4) methylester **(20)** is the biogenetic precursor of the leukotrienes LTC_4, LTD_4, and LTE_4 which are important natural mediators of allergic asthma[603]. Arene oxides have been postulated to be intermediates in the metabolism of aromatic compounds to phenols[604]. The ultimate carcinogenic metabolites of polycyclic aromatic hydrocarbons are tetrahydrodiol epoxides[605]. The biological activities of aflatoxin B_1 and precocenes are due to oxiranes derived from them[606]. Because of the biological importance of oxirane, the synthesis of 1-[1-oxido-2-(3-,4-)pyridinyl]-2-methyloxiranes and their reaction with sulfur, oxygen and nitrogen nucleophiles was previously investigated in this research group[607,608]. It was therefore of interest to extend this study to include a new class of 1-(2-pyridinyl)-2-alkylcarbonyloxiranes and determine their cytotoxicities in the P388 leukemia screen[609].



13

$R^1 = R^2 =$ H, Cl



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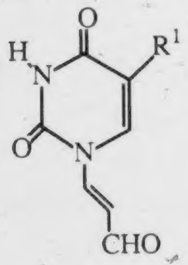
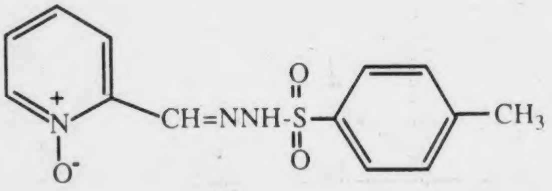


15

$R^1 =$ H, F, CH_3, CF_3



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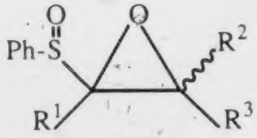
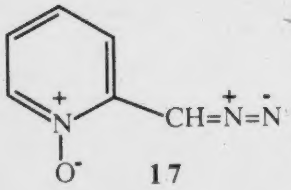


18

$R^1 =$ alkyl, arylalkyl
$R^2 =$ alkyl, aryl
$R^3 =$ H, CH_3



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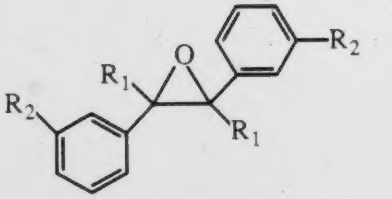
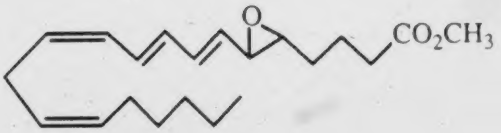


19

R_1=alkyl, R_2= OH, OAc



20

LTA_4

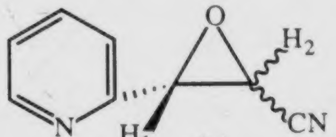
Table 44. Antitumor activity for compounds with 12 or less carbon[602].

GROUPS	NCI ACTIVE	NCI TESTED	NORMALIZED ACTIVITY RATIO
Hydroxy	1	2296	0.03
Ethers	2	266	0.7
Epoxides	7	33	9.2
Aldehydes	2	133	0.65
Acetals, ketals, ketenes	0	1	0
Ketones	1	463	0.09
Quinones	0	65	0
Carboxylic acids	0	701	0
Ester or lactones	3	1278	0.10
Acyl halides, anhydrides	2	128	0.8
Amides	8	893	0.38
Imides	0	14	0
Hydrazides	7	151	2.0
Hydroxamic acids	2	38	2.3
Azides	1	17	2.5
Cyanides	3	135	0.96
Diazo	0	0	0
Diazonium	0	0	0
Sulfoxides	4	145	1.2
Sulfinic acids	0	3	0
Sulfonic acid esters	8	90	4.0

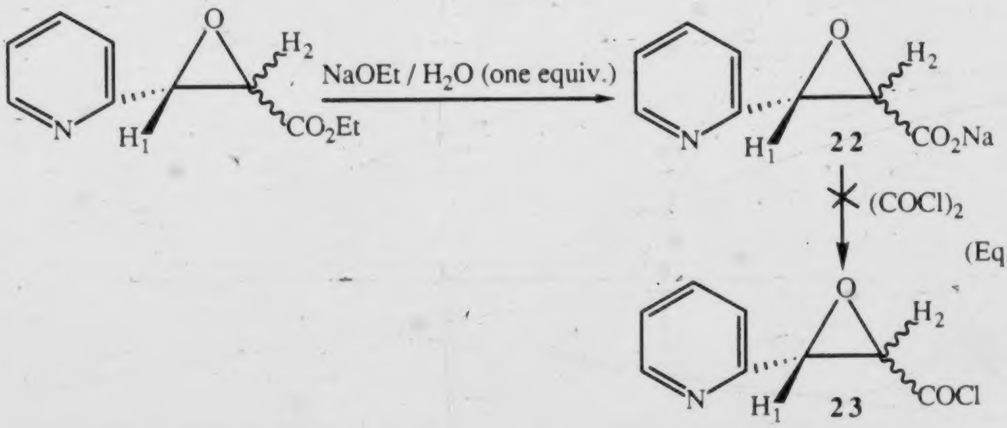
$$\text{NORMALIZED ACTIVITY RATIO} = \frac{\text{NO. ACTIVES IN CLASS}}{\text{TOTAL NO. IN CLASS}} \div \frac{\text{ALL NCI ACTIVES}}{\text{ALL NCI COMPOUNDS}}$$

3.2.0.0.0 PREPARATION OF *Trans*- and *Cis*-1-(2-PYRIDINYL)-1,2-EPOXYALKAN-3-ONES.

α,β-Epoxyketones have been synthesized starting from α,β-epoxynitriles (Eq. 14). However, when R^1 was 2-pyridinyl (**21**), the epoxynitrile was unstable and decomposed at room temperature. Although, the reaction of α,β-epoxyacyl chlorides with organometallic reagents (Eq.13) is often a suitable procedure, when R^1 was 2-pyridinyl, the reaction of (**22**) with oxalyl chloride gave a polymerized product rather than the desired α,β-epoxycarbonyl chloride (**23**) (Eq. 17).

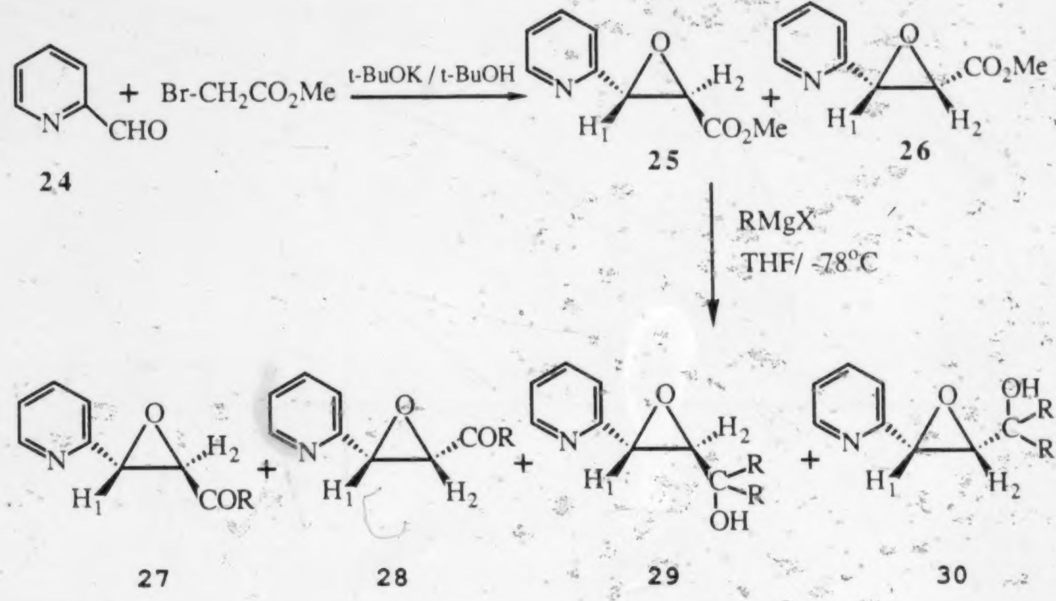


21



(Eq.17)

The method of choice to synthesize *trans*- and *cis*-1-(2-pyridinyl)-1,2-epoxyalkan-3-ones was reaction of α,β-epoxyesters with Grignard reagents at low temperature. The Darzen's reaction of 2-pyridinecarboxaldehyde (**24**) with methyl bromoacetate in the presence of potassium t-butoxide in t-butanol afforded a 1:2 mixture of the *trans*-**(25)** and *cis*-methyl 3-(2-pyridinyl)-2,3-epoxypropanoate **(26)** stereoisomers[610]. The ratio of isomers can be changed by using $LiN(SiMe_3)_2$ as base at -78 °C which affords predominantly the *trans*-isomer (86%)[611]. Further reaction of a 1:1 mixture, obtained after purification of **(25)** and **(26)**, with n-butylmagnesium bromide afforded a mixture of *trans*-**(27a)** and *cis*-1-(2-pyridinyl)-1,2-epoxyheptan-3-one **(28a)** together with traces of the *trans*-**(29a)** and *cis*-**(30a)** alcohols, which were separated by silica gel column chromatography. Similar reactions of **(25)** and **(26)** with n-hexyl-, n-decyl-, and n-hexadecylmagnesium bromide yielded the corresponding *trans*-**(27b-d)**, *cis*-**(28b-d)**; *trans*-**(29b-d)** and *cis*-**(30b-d)** alcohols as outlined in Scheme 30. The analytical data for *trans*-**(27a-d)** and *cis*-**(28a-d)** are summarized in Table 45. The stereochemistry of the products was readily assigned since the ^1H nmr spectra exhibited $J_{1,2}$ coupling constants of 1.5 and 4.5 Hz for *trans*-**(27)** and *cis*-**(28)**, respectively,[607,608,610] as summarized in Table 46. Karplus has shown that the mutual spin-spin interaction experienced by the protons of a HCCH system is dependent upon the vicinal dihedral angle[612,613]. In the case of oxiranes, the coupling constants are smaller than would be predicted on the basis of such a correlation. It is noteworthy that J_{cis} is always significantly greater than J_{trans} for any given set of epoxide stereomers. However, the absolute values of J can not be singly used to assign ring substituent stereochemistry. This is based on the fact that the coupling constants for oxiranes are not dependent solely on the dihedral angle.

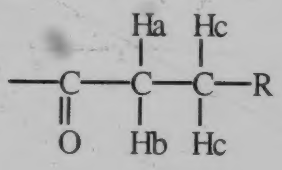


R = a) n-butyl; b) n-hexyl;

c) n-decyl; and d) n-hexadecyl.

Scheme 30. Synthesis of *trans*- and *cis*-1-(2-pyridinyl)-1,2-epoxyalkan-3-ones.

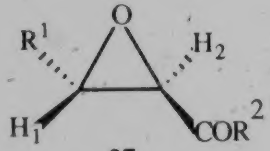
Other variables such as bond length and electronegativity, as well as hybridization, must be taken into account if reliable quantitative predictions are to be made[614]. Abundant data summarizing the coupling constants for substituted oxiranes have been compiled[615,616]. The magnitude of vicinal coupling constants for *trans*- and *cis*-oxiranes decreases linearly as the electronegativity of substituents increases[615]. The chemical shift for proton H_1 adjacent to the pyridine ring appears at lower field than H_2 for both *cis*- and *trans*-oxiranes (Table 46). This low field shift has been attributed to a ring current effect of the pyridine ring[617]. The chemical shifts for the *cis* protons of **28**(**a-d**) appear at lower field (δ 0.1-0.3) than those for the corresponding *trans* **27**(**a-d**) isomers. This can be explained by the direction of the polarization effect due to the electric dipole moment of one CH proton on the other CH proton[616]. The ^1H nmr and ir spectroscopic data for *trans*-**27**(**a-d**) and *cis*-**28**(**a-d**) are summarized in Tables 47 and 48, respectively. The oxirane ring has C-C bond properties intermediate between those of a saturated C-C and olefinic C=C bond. It is expected that the stretching frequency of a carbonyl group in α,β-epoxyketones will be intermediate between the frequencies reported for saturated and α,β-unsaturated ketones[618]. The ir spectra displayed carbonyl stretching frequencies at 1712 cm^{-1} for *trans*-**27**(**a-d**) and at 1720 cm^{-1} for *cis*-**28**(**a-d**) stereoisomers. The oxirane C-O stretching band appeared at 1212 cm^{-1} for both isomers. The ^1H nmr spectra for **27** and **28** exhibited two overlapping multiplets in the δ 2.4-2.5 range which were assigned to the non-equivalent protons of the -$\underline{\mathbf{CH_2}}$- moiety adjacent to the carbonyl group (-CO-$\underline{\mathbf{CH_2}}$-R) (**31**).

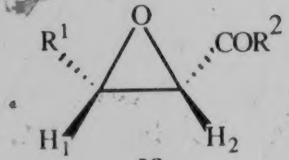


$$-\underset{\underset{O}{\|}}{C}-\overset{Ha}{\underset{Hb}{C}}-\overset{Hc}{\underset{Hc}{C}}-R$$

31

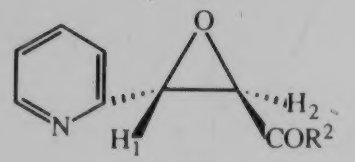
Table 45. Stereoisomers, and analytical data for compounds (**27a-d**) and (**28a-d**).


27

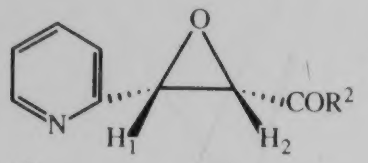

28

Comp.	R^1	R^2	Stereoisomer	Formula	Microanalyses: Found (calc.)		
					C%	H%	N%
27a	2-pyridinyl	n-C_4H_9	trans	$C_{12}H_{15}NO_2$	70.37 (70.24)	7.53 (7.31)	6.52 (6.82)
28a	2-pyridinyl	n-C_4H_9	cis	$C_{12}H_{15}NO_2$	69.89 (70.24)	7.30 (7.31)	6.62 (6.82)
27b	2-pyridinyl	n-C_6H_{13}	trans	$C_{14}H_{19}NO_2$	71.73 (72.07)	8.20 (8.21)	5.83 (6.00)
28b	2-pyridinyl	n-C_6H_{13}	cis	$C_{14}H_{19}NO_2$	72.21 (72.07)	8.26 (8.21)	5.86 (6.00)
27c	2-pyridinyl	n-$C_{10}H_{21}$	trans	$C_{18}H_{27}NO_2$	74.69 (74.70)	9.10 (9.40)	4.56 (4.83)
28c	2-pyridinyl	n-$C_{10}H_{21}$	cis	$C_{18}H_{27}NO_2$	74.62 (74.70)	9.32 (9.40)	4.62 (4.83)
27d	2-pyridinyl	n-$C_{16}H_{33}$	trans	$C_{24}H_{39}NO_2$	77.00 (77.16)	10.64 (10.52)	3.51 (3.74)
28d	2-pyridinyl	n-$C_{16}H_{33}$	cis	$C_{24}H_{39}NO_2$	76.83 (77.16)	10.45 (10.52)	3.44 (3.74)

Table 46. Chemical shifts and $J_{1,2}$ coupling constants for *trans* -1-(2-pyridinyl)-1,2-epoxyalkan-3-ones (**27**) and *cis* -1-(2-pyridinyl)-1,2-epoxyalkane-3-ones (**28**).



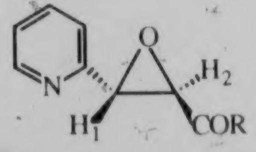
27



28

R^2	Comp.	Chemical shifts ^1H NMR δ **trans**		Comp.	Chemical shifts ^1H NMR δ **cis**		Coupling constants $J_{1,2}$ Hz	
		H_1	H_2		H_1	H_2	**trans**	**cis**
n-C_4H_9	**27a**	4.3	3.72	**28a**	4.4	4	1.5	4.5
n-C_6H_{13}	**27b**	4.16	3.72	**28b**	4.4	4	1.5	4.5
n-$C_{10}H_{21}$	**27c**	4.16	3.72	**28c**	4.4	4	1.5	4.5
n-$C_{16}H_{33}$	**27d**	4.14	3.70	**28d**	4.4	4	1.5	4.5

Table 47. Ir[a,b] and ^1H nmr[c] spectral data for *trans* -1-(2-pyridinyl)-1,2-epoxyalkan-3-ones (**27a-d**).



27 (a-d)

Comp.	ir (cm^{-1}) (C=O, C-O)	^1H nmr δ [ppm]
27a	1712, 1212[a]	0.9 (t, J= 7 Hz, 3H, CH_3); 1.31 (m, 2H, $\underline{CH_2}CH_3$); 1.6 (m, 2H, $\underline{CH_2}CH_2CH_3$); 2.5 (m, 2H, $CO\underline{CH_2}$); 3.72 (d, $J_{1,2}$= 1.5Hz, 1H, H--2); 4.3 (d, $J_{1,2}$= 1.5 Hz, 1H, H-1); 7.28 (m, 2H, pyridinyl , H-3, H-5); 7.73 (d, $J_{3,4}$= 8.0 Hz of $d_{4,5}$= 8Hz Hz, 1H, pyridinyl H-4); 8.6 (d, $J_{5,6}$= 5Hz of d, $J_{4,6}$= 1.6 Hz, 1H, pyridinyl H-6).
27b	1712, 1212[b]	0.9 (t, J= 7 Hz, 3H, H-9); 1.25 (m, 6 H, H-6 to H-8); 1.62 (m, 2H, H-5); 2.5 (m, 2H, H-4); 3.72 (d, $J_{1,2}$= 1.5 Hz, 1H, H-2); 4.16 (d, $J_{1,2}$= 1.5 Hz, 1H, H-1); 7.25 (m, 2H, pyridinyl H-3, H-5); 7.76 (d, $J_{4,5}$= 8 Hz, of d, $J_{3,4}$= 8Hz of d, $J_{4,6}$= 1.5 Hz, 1H, pyridinyl, H-4); 8.6 (d, $J_{5,6}$= 5 Hz of d, $J_{4,6}$= 1.5 Hz, 1H, pyridinyl H-6).

Table 47. (cont.)

27c	1712, 1212[b]	0.9 (t, J= 7 Hz, 3H, H-13); 1.3 (m, 14 H, H-6 to H-12); 1.65 (m, 2H, H-5); 2.5 (m 2H, H-4); 3.72 (d, $J_{1,2}$= 1.5 Hz, 1H, H-2); 4.16 (d, $J_{1,2}$= 1.5 Hz, 1H, H-1); 7.28 (m, 2H, pyridinyl H-3, H-5); 7.73 (d, $J_{4,5}$= 8 Hz, of d, $J_{3,4}$= 8 Hz of d, $J_{4,6}$= 1.5 Hz, 1H, pyridinyl H-4) ; 8.6 (d, $J_{5,6}$= 5 Hz of d, $J_{4,6}$= 1.6Hz, 1H, pyridinyl H-6).
27d	1712, 1212[b]	0.84 (t, J= 7 Hz, 3H, H-19); 1.25 (m, 26 H, H-6 to H-18); 1.65 (m, 2H, H-5); 2.5 (m, 2H, H-4); 3.7 (d, $J_{1,2}$= 1.5 Hz, 1H, H-2); 4.14 (d, $J_{1,2}$= 1.5 Hz, 1H, H-1); 7.24 (d, $J_{4,5}$= 8 Hz, of d, $J_{5,6}$= 5 Hz, 1H, pyridinyl H-5); 7.46 (d, $J_{3,4}$= 8 Hz, 1H, pyridinyl H-3); 7.72 (d, $J_{3,4}$= 8 Hz, of d, $J_{4,5}$= 8 Hz of d, $J_{4,6}$= 1.6 Hz, 1H, pyridinyl H-4); 8.6 (d, $J_{5,6}$= 5 Hz of d, $J_{4,6}$= 1.6 Hz, 1H, pyridinyl H-6).

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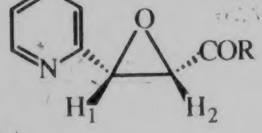
[a]Film, [b]KBr, [c]$CDCl_3$.

Table 48. Ir^{a,b}and ^{1}H nmr^{c} spectral data for *cis* -1-(2-pyridinyl)-1,2-epoxyalkan-3-ones (**28a-d**).



28 (a-d)

Comp.	ir (cm^{-1}) (C=O, C-O)	^{1}H nmr δ [ppm]
28a	1720, 1212^{a}	0.8 (t, J= 7 Hz, 3H, CH_3); 1.12 (m, 2H, $\underline{CH_2}CH_3$); 1.4 (m, 2H, $\underline{CH_2}CH_2CH_3$); 2.45 (m, 2H, $CO\underline{CH_2}$); 4.0 (d, $J_{1,2}$= 4.5Hz, 1H, H--2); 4.4 (d, $J_{1,2}$= 4.5 Hz, 1H, H 1); 7.24 (d, $J_{4,5}$= 8Hz of d, $J_{5,6}$= 5 Hz, 1H, pyridinyl H-5); 7.46 (d, $J_{3,4}$= 8Hz, 1H, pyridinyl H-3); 7.72 (d, $J_{3,4}$= 8.0 Hz of d,$_{4,5}$= 8Hz of d, $J_{4,6}$= 2 Hz, 1H, pyridinyl H-4); 8.6 (d, $J_{5,6}$= 5Hz , 1H, pyridinyl H-6).
28b	1720, 1212^{a}	0.8 (t, J= 7 Hz, 3H, H-9); 1.20 (m, 6H, H-6 to H-8); 1.30 (m, 2H, H-5); 2.4 (m, 2H, H-4); 4.0 (d, $J_{1,2}$= 4.5 Hz, 1H, H-2); 4.4 (d, $J_{1,2}$= 4.5 Hz, 1H, H-1); 7.25 (d, $J_{4,5}$= 8Hz of d, $J_{5,6}$= 5 Hz, 1H, pyridinyl H-5); 7.46 (d, $J_{3,4}$= 8Hz, 1H, pyridinyl H-3); 7.72 (d, $J_{3,4}$= 8 Hz of d, $J_{4,5}$=

Table 48. (cont.)

		8Hz of d, $J_{4,6}$= 1.5 Hz, 1H, pyridinyl H4); 8.6 (d, $J_{5,6}$= 5 Hz of d, $J_{4,6}$= 1.5 Hz, 1H, pyridinyl H-6).
28c	1721, 1212^b	0.96 (t, J= 7 Hz, 3H, H-13); 1.0-1.4 (m, 16 H, H-5 to H-12); 2.4 (m, 2H, H-4); 4.0 (d, $J_{1,2}$= 4.5 Hz, 1H, H-2); 4.4 (d, $J_{1,2}$= 4.5 Hz, 1H, H-1); 7.24 ($J_{4,5}$= 8Hz of d, $J_{5,6}$= 5Hz, 1H, pyridinyl H-5); 7.46 (d, $J_{3,4}$= 8Hz, 1H, pyridinyl H-3); 7.72 (d, $J_{3,4}$= 8Hz of d, $J_{4,5}$= 8Hz of d, $J_{4,6}$= 1.6 Hz, 1H, pyridinyl, H-4); 8.6 (d, $J_{5,6}$= 5 Hz of d, $J_{4,6}$= 1.6 Hz, 1H, pyridinyl H-6).
28d	1720, 1212^b	0.91 (t, J= 7 Hz, 3H, H-19); 1.0-1.5 (m, 28 H, H-5 to H-18); 2.5 (m, 2H, H-4); 4.0 (d, $J_{1,2}$= 4.5 Hz, 1H, H-2); 4.4 (d, $J_{1,2}$= 4.5 Hz, 1H, H-1); 7.24 (d, $J_{4,5}$= 8 Hz of d, $J_{5,6}$= 5 Hz, 1H, pyridinyl, H-5); 7.46 (d, $J_{3,4}$= 8 Hz, 1H, pyridinyl H-3); 7.72 (d, $J_{3,4}$= 8 Hz of d, $J_{4,5}$= 8Hz of d, $J_{4,6}$= 1.6 Hz, 1H, pyridinyl H-4); 8.6 (d, $J_{5,6}$= 5 Hz of d, $J_{4,6}$= 1.6Hz, 1H, pyridinyl H-6).

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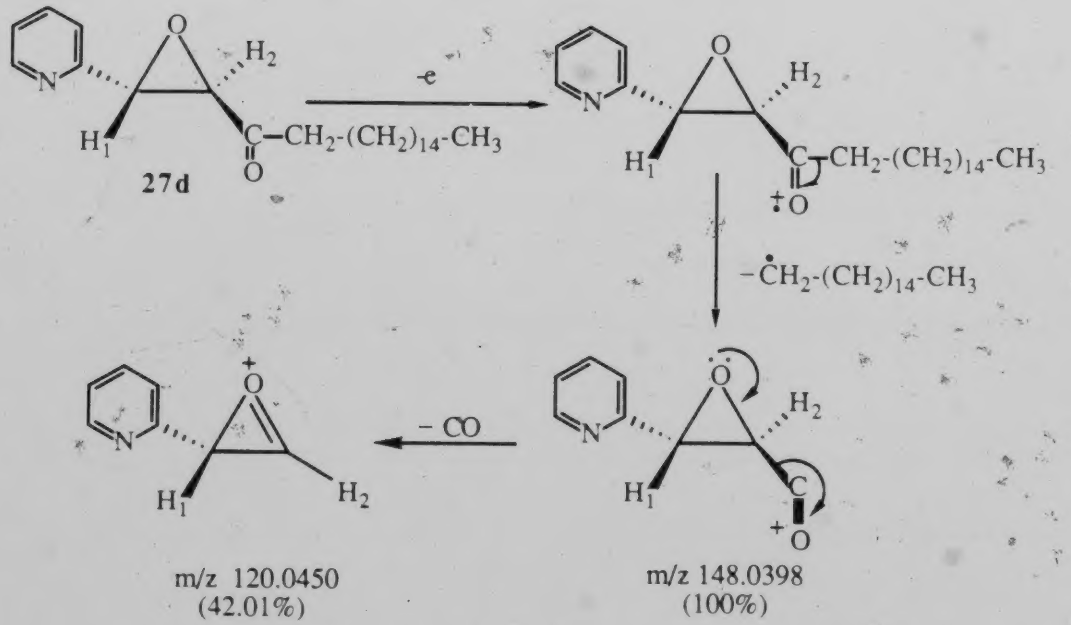
^{a}Film, ^{b}KBr, ^{c}CDCl$_3$

The mass spectrum of *trans*-1-(2-pyridinyl)-1,2-epoxynonadecan-3-one (**27d**) exhibited a molecular ion at m/z 373.2974 (4.9%). The major fragmentation pathways for **27d** are shown in Scheme 31. The base peak at m/z 148.0398 (100%) arises from cleavage of the -C-CO- bond to give an acylium ion from which carbon monoxide is subsequently expelled to form an ion at m/z 120.0450 (42.01%) as illustrated in Path a. There was no evidence for a McLafferty rearrangement involving the ketone side chain or fragmentation of an alkyl acylium side chain ion. The only hydrogen rearrangement observed was elimination of ketene to give an ion at m/z 121.0525 (37.13%) as illustrated by Path b.

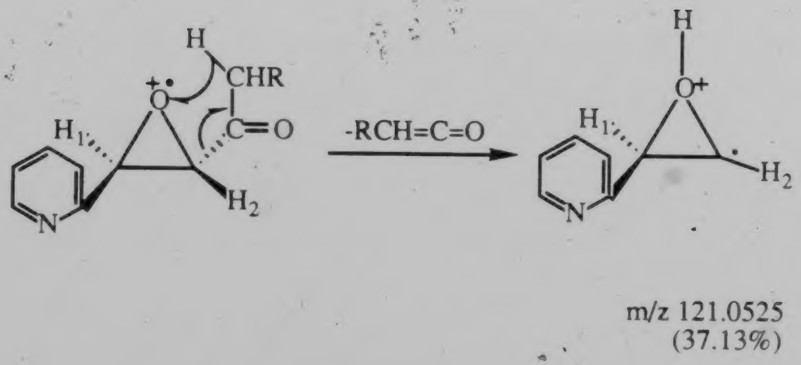
3.3.0.0.0 PHARMACOLOGICAL RESULTS.

The *trans*-(**27**) and *cis*-1-(2-pyridinyl)-2-alkylcarbonyloxiranes (**28**) were investigated to determine the stereochemical effect of the R^1 (2-pyridinyl) and R (alkyl) substituents upon cytotoxicity. It has been reported that *trans*-(**32**) and *cis*-methyl 3-(1-oxido-2-pyridinyl)-2,3-epoxypropanoates (**33**) undergo regiospecific and stereospecific reactions with amine nucleophiles at the C-2 position to yield the respective 2R,3R or 2S,3S (*threo*) and 2R,3S or 2S,3R (*erythro*) β-aminoalcohol diastereomers as presented in Scheme 32[610].

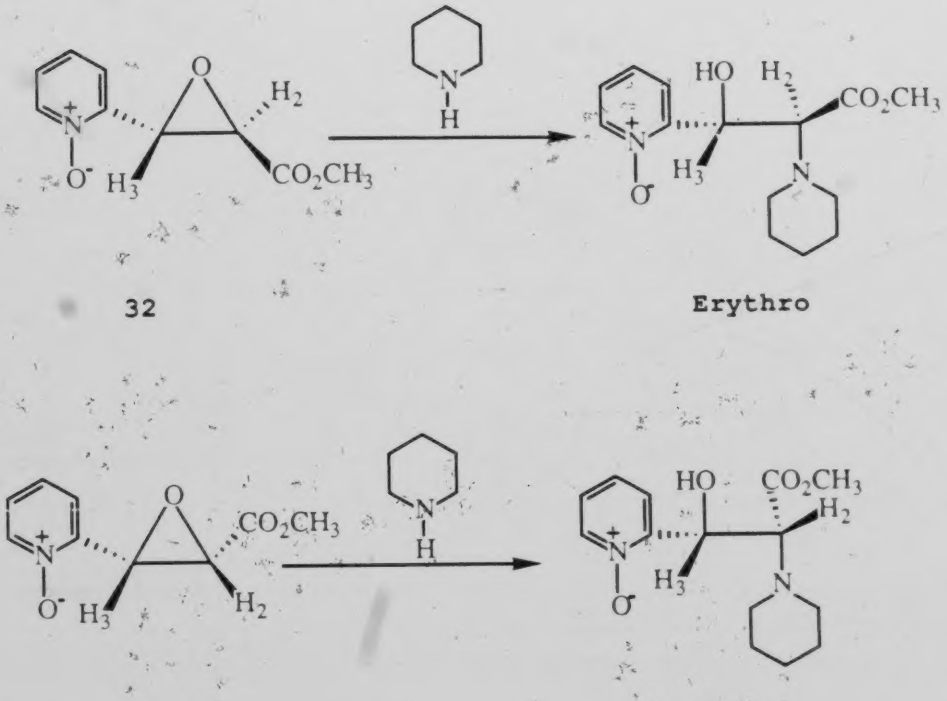
Path a.


N
O
H1
H2
27d
C—CH2-(CH2)14-CH3
O
-e
+O
-ĊH2-(CH2)14-CH3
- CO
+
C
m/z 120.0450
(42.01%)
m/z 148.0398
(100%)

Patb b.


H
CHR
+•
O
C=O
H1
H2
N
-RCH=C=O
O+
m/z 121.0525
(37.13%)

Scheme 31. The major fragmentation pathways for *trans*-1-(2-pyridinyl)-1,2-epoxynonadecan-3-one (27d).


O
H2
CO2CH3
O⁻
H3
N
H
HO
H2
CO2CH3
H3
O⁻
N
O
CO2CH3
H3
H2
N
H
HO
CO2CH3
H2
H3
O⁻
N

32

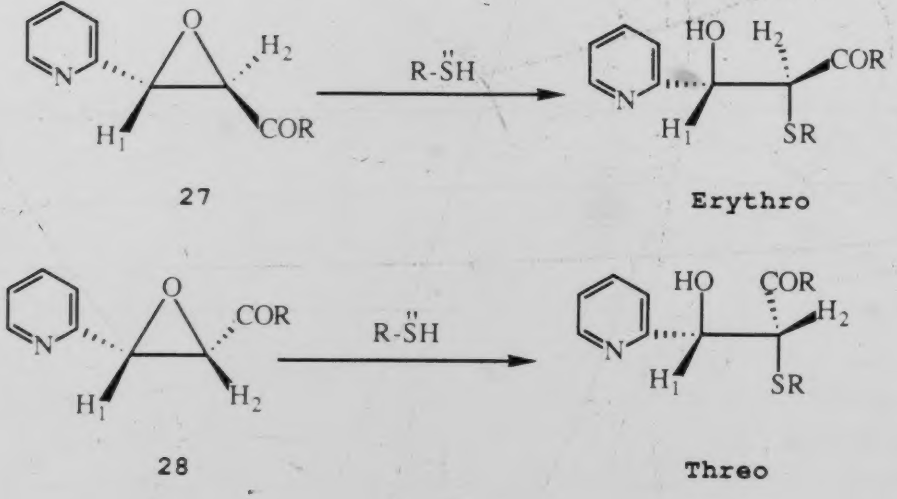
Erythro

33

Threo

Scheme 32. The mechanism of ring opening of the *trans*-(**32**) and *cis*-methyl-3-(1-oxido-2-pyridyl)-2,3-epoxypropanoates (**33**).

The relative reaction rates of the Michael PhCH=CH-R compounds with thiols is R = COMe $\geq$ R = CO_2Me > R = $CONH_2$[619]. It was expected that oxiranes (**27**) and (**28**) having electron-attracting carbonyl and pyridinyl substituents would be highly activated to regiospecific attack by cellular thiol nucleophiles (R-SH) at the C-2 position as illustrated in Scheme 33.



Scheme 33. The mechanism of ring opening of the *trans*-(**27**) and *cis*-1-(2-pyridinyl)-2-alkylcarbonyloxiranes (**28**).

The test results (Table 49) indicate that the stereochemistry of the oxiranyl substituents and/or size of the R alkyl substituents of (**27**) and (**28**) are determinants of cytotoxic activity. A comparison of the relative activities of *trans*-**27** with the corresponding *cis*-**28** isomer (Fig.30) indicated that n-butyl **27a** > **28a***, n-hexyl **28b** ~ **27b****, n-decyl **28c** > **27c*** and n-hexadecyl **28d** > **27d***. The *trans*-isomer **27a** was more active than the *cis*-isomer **28a** for compounds having a smaller n-butyl R substituent, whereas the *cis*-isomers (**28c** and **28d**) were more active than the corresponding *trans*-isomers (**27c** and **27d**), for compounds having larger n-decyl and n-hexadecyl R substituents. It is plausible that the increased steric effect exhibited by the 2-pyridyl and R substituents for compounds possessing the larger n-decyl and n-hexadecyl substituents is responsible for the greater activity of the *cis* isomer, relative to the corresponding trans isomer, which would result in a more facile reaction with cellular nucleophiles, as illustrated in Scheme 33. A comparison of the relative activities of the *trans*-**27** products possessing a variety of R alkyl substituents at concentrations of 10 μg/ml indicated n-butyl **27**a ~ n-hexyl **27**b** > n-decyl **27**c* > n-hexadecyl **27**d* (Fig.31). These results indicate that increasing the size of the R alkyl substituents of *trans*-**27** decreases activity probably due to increased steric effects. Increasing the size of the R alkyl substituent of *trans*-**27** would be expected to decrease the rate of attack by cellular nucleophiles at the C-2 position of **27**. On the other hand, the relative potency order for the **cis**-28 compounds was n-decyl **28c** > n-hexyl **28b***** > n-butyl **28a*** > n-hexadecyl **28d***** (Fig.32). The effect of the R substituent on lipophilicity is not expected to be a significant determinant of activity, since the relative potency sequences for *trans*-**27** and *cis*-**28** would be similar if lipophilicity was the major determinant of activity.

---

*ANOVA (analysis of variants) indicated the result is statistically significant ($p < 0.001$).

** ANOVA indicated the result is not statistically significant ($p > 0.05$).

*** ANOVA indicated the result is statistically significant ($p < 0.05$).

Table 49. *In vitro* cytotoxicity of 1-(2-pyridinyl)-1,2-epoxyalkan-3-ones **27a-d** and **28a-d** against mouse L1210 leukemia cells.

Compound	% Survival ± SD[a]	
	10 μg/ml	1 μg/ml
27a	34.64 ± 3.83	96.21 ± 1.87
28a	69.32 ± 4.59	99.12 ± 1.45
27b	38.69 ± 4.02	95.33 ± 3.47
28b	35.67 ± 2.70	95.74 ± 6.05
27c	78.82 ± 3.11	93.00 ± 5.48
28c	28.43 ± 1.45	92.54 ± 3.32[b]
27d	96.09 ± 3.57	96.25 ± 2.75
28d	78.47 ± 6.47	98.71 ± 1.14[c]
Melphalan[d]	0.00	2.82 ± 0.68[e]

[a] The result is mean value ± SD for three experiments.

[b] ED_{50}= 5.6 μg/ml (1.93 x 10^{-3} μM).

[c] ED_{50}= 10.2 μg/ml (2.73 x 10^{-2} μM).

[d] 4-[N-bis-(2-chloroethyl)amino]phenylalanine.

[e] ED_{50}= 0.15 μg/ml (5.45 x 10^{-4} μM).

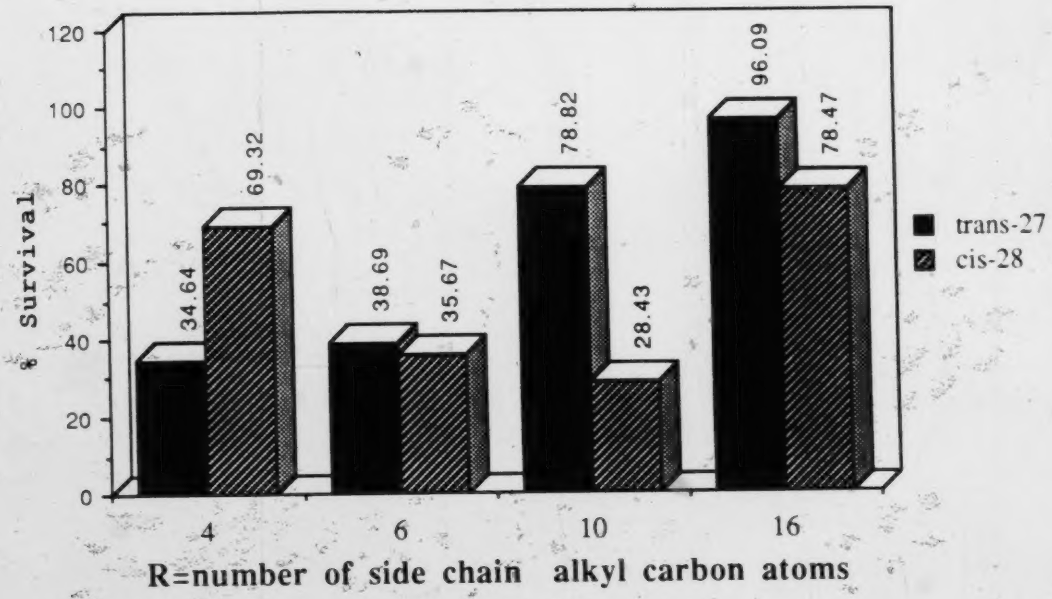


Fig.30. Structure activity relationship comparisons for *trans*-**27a-d** and*cis*-**28a-d** based on the length of alkyl substituent **R** (% survival for a 10 mg/ml concentration using the *in vivo* L1210 leukemia screen).

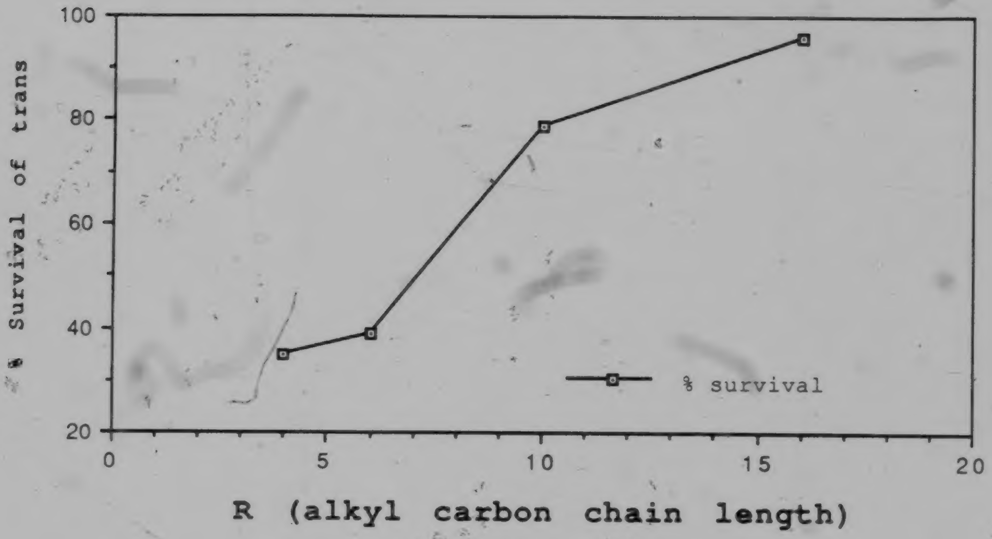


Fig.31. SARs for *trans*-1-(2-pyridinyl)-1,2-epoxyalkan-3-ones (**27a-d**).

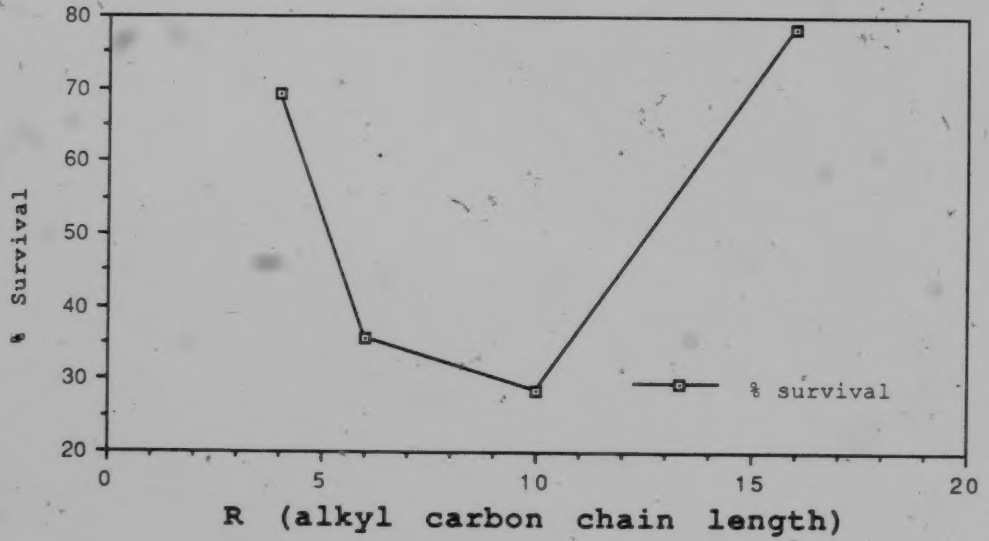


Fig.32. SARs for *cis*-1-(2-pyridinyl)-1,2-epoxyalkan-3-ones (**28a-d**).

4.0.0.0.0 EXPERIMENTAL.

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined for solutions in deuterochloroform unless otherwise stated with TMS as internal standard with a Varian EM-360A or Bruker AM-300 spectrometer. Mass spectra were measured with an AEI-MS-50 mass spectrometer. Infrared spectra (potassium bromide unless otherwise noted) were taken on a Nicolet 5DX spectrometer. All of the products gave rise to a single spot on TLC using a solvent system of low, medium and high polarity. Analyses of all compounds prepared in this study were within ± 0.40% of the theoretical values for C, H, and N. Flash column chromatography was carried out utilizing Merck 60 silica gel. Column chromatography was performed using JT Baker 60-200 mesh silica gel. Preparative thin layer chromatography was performed using Kieselgel silica gel DF-5 (Camag) plates, 1 mm in thickness. All Grignard reactions were carried out using glassware that was oven-dried for 24 hours prior to use, under an atmosphere of nitrogen. Dry nitrogen gas was obtained by passage through concentrated sulfuric acid, solid potassium hydroxide and then anhydrous calcium sulfate.

4.1.0.0.0 SOLVENTS AND REAGENTS.

Tetrahydrofuran was dried, by heating at reflux in the presence of sodium metal and benzophenone under a nitrogen atmosphere, and distilled immediately prior to use. Alkyl halide reagents were double-distilled and stored under an atmosphere of nitrogen prior to use.

4.2.0.0.0 PREPARATION OF *trans*-(27a) and *cis*-1-(2-PYRIDINYL) 1,2-EPOXYHEPTAN-3-ONE (28a).

A solution of n-butylmagnesium bromide, prepared by the dropwise addition of 1-bromobutane (1.68 g, 12.3 mmol) in 5 mL dry tetrahydrofuran to magnesium metal (0.3 g, 12.3 mmol) suspended in 2 mL dry tetrahydrofuran under a nitrogen atmosphere at 25 °C with stirring until all the magnesium metal had reacted, was added to a solution of **25** and **26** (2 g, 11.17 mmol, ratio 1:1)[148] in 60 mL dry tetrahydrofuran under a nitrogen atmosphere at -78 °C. The reaction was allowed to proceed at -78 °C for 4 h, at which time tlc indicated the absence of **25** and **26**, and then water (20 mL) was added. The reaction mixture was allowed to warm to 25 °C, the solvent was removed *in vacuo* and the residue was dissolved in 5% aqueous hydrochloric acid (20 mL). Extraction with ether (4 x 40 mL), drying (Na_2SO_4) and removal of the solvent *in vacuo* gave an oil (2 g). Purification by elution from a silica gel column (3 x 40 cm) with ether:hexane (80:20 v/v) as eluant afforded a mixture consisting of predominantly **27a** contaminated with traces of *trans*- and *cis*-t-alcohol products resulting from further reaction of **27a** and **28a**, respectively with n-butylmagnesium bromide. Further elution gave **28a** (0.7 g, 30.5%, as an oil). The mixture containing predominantly **27a** obtained above was separated on 20 x 20 cm silica gel G plates, 1 mm in thickness, with ether:hexane (60:40 v/v) as development solvent using the multiple development TLC technique. Extraction of the band having R_f 0.8 with methanol afforded **27a** (0.8 g, 34.4%, as an oil).

4.3.0.0.0 PREPARATION OF *trans*-(27b) and *cis*-1-(2-PYRIDINYL)-1,2-EPOXYNONAN-3-ONE (28b).

Compounds **27b** and **28b** were prepared using the procedure outlined in section 4.2.0.0.0. Products **27b** and **28b** were separated on a silica gel column using ether:hexane (70:30 v/v) as eluant. The *trans*-product **27b** was purified further by preparative multiple development tlc using ether:hexane (1:1 v/v) as development solvent (R_f 0.8).

27b, mp 44°C, 30.5% yield.

28b, as an oil, 26.5% yield.

4.4.0.0.0 PREPARATION OF *trans*-(27c) and *cis*-1-(2-PYRIDINYL)-1,2-EPOXYTRIDECAN-3-ONE (28c).

Compounds **27c** and **28c** were prepared according to the procedure outlined in section 4.2.0.0.0, except the preparation of n-decylmagnesium bromide required heating under reflux to complete the reaction and dry tetrahydrofuran (20 mL) was added, prior to reaction with **25** and **26**, to prevent precipitation of the Grignard reagent. Products **27c** and **28c** were separated on a silica gel column using ether:hexane (60:40 v/v) as eluant. The *trans*- product **27c** was purified by preparative multiple development tlc using ether:hexane (1:1 v/v) as development solvent (R_f 0.8).

27c, mp 49°C, 25% yield.

28c, mp 34°C, 21.5% yield.

4.5.0.0.0 PREPARATION OF *trans*-(27d) and *cis*-1-(2-PYRIDINYL)-1,2-EPOXYNONADECAN-3-ONE (28d).

The synthesis of **27d** and **28d** was carried out using the method described in section 4.2.0.0.0. The preparation of n-hexadecylmagnesium bromide required addition of a crystal of iodine as catalyst, heating under reflux to complete the reaction and dry tetrahydrofuran (30 mL) was added, prior to reaction with **25** and **26**, to prevent precipitation of the Grignard reagent. The reaction of Grignard reagent with **25** and **26** was allowed to proceed for 8 h at -78 ^{o}C. Products **27d** and **28d** were separated on a silica gel column using ether:hexane. (70:30 v/v) as eluant. The *trans*-product **27d** was purified by preparative multiple development tlc using ether:hexane (1:1 v/v) as development solvent (R_f 0.8).

27d, mp 69^{o}C, 20% yield.

28d, mp 59^{o}C, 12.5% yield.

4.6.0.0.0 PHARMOCOLOGICAL EVALUATION *In vitro* L1210 CYTOTOXIC SCREEN.

The pharmacological evaluation was performed by Dr. T. Allen, Department of Pharmacology, University of Alberta.

Mouse L1210 leukemia cells were cultivated as a suspension in Fisher's medium supplemented with 10% heat-inactivated horse serum and incubated at 37 ^{o}C in a humidified 5% CO_2 atmosphere to prepare a cell stock solution. The number of cells/mL of medium was determined using a Model ZF Coulter counter 48 h after incubation. The test compound was dissolved in saline:ethanol (1:1 v/v) and 20 mL of this solution was added to test wells containing 2 mL of suspended L1210 cells (10^5

cells/mL) such that 2 mL of the cell suspension had a test compound concentration of 50, 10 and 1 µg/mL of medium, respectively. Control wells were identical, except that the test compound was absent. Compounds for which ED_{50} values were obtained had the following test compound concentration (µg/mL of medium): **28c** and **28d** (50, 25, 10, 5, 2.5 and 1.25), and melphalan (10, 1, 0.5, 0.25, 0.1 and 0.05). All tests and controls were grown in triplicate. The % cell survival was calculated using the formula:

$$\% \text{ Survival} = \frac{T_{48}-T_0}{C_{48}-C_0} \times 100$$

where T_{48} is the means number of living cells/mL for each test drug concentration at 48 h, T_0 is the mean number for the test wells at time zero (normally 10^5), C_{48} is the mean number for the control at 48 h and C_0 the mean number for the control at time zero (normally, $T_0 = C_0 = 10^5$ cells/mL).

5.0.0.0.0 BIBLIOGRAPHY.

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